

C O N T E N T S

The American Journal of Medicine

VOL. X APRIL, 1951 No. 4

Editorial

- Collagen Disease PAUL KLEMPERER 405

Clinical Studies

- Detection of Uneven Alveolar Ventilation during a Single Breath of Oxygen
JULIUS H. COMROE, JR. AND WARD S. FOWLER 408

The authors describe an elegant method for detecting uneven distribution of inspired gas in the lungs, suitable for recognition of emphysema and a variety of other pulmonary diseases in which this abnormality may occur.

- Effect of Nitroglycerine on the Cardiovascular System of Normal Persons
RENÉ WÉGRIA, JOHN L. NICKERSON, ROBERT B. CASE AND JAMES F. HOLLAND 414

Nitroglycerine in the ordinarily employed dosage was found to produce a substantial increase in cardiac output, presumably as a result of vasodilation, without change in blood pressure. Increase in coronary flow by nitroglycerine therefore involves an increase in cardiac work, an undesirable effect in the presence of myocardial infarction.

- The Natural Course of Rheumatoid Arthritis and the Changes Induced by ACTH
JOSEPH E. GIANIRACUSA, MARIAN W. ROPES, J. PETER KULKA AND
WALTER BAUER 419

This is a detailed long-term study of a patient with rheumatoid arthritis. A 130-day course of ACTH produced the usual dramatic but incomplete reversal of disease activity without eradication of the underlying disease process.

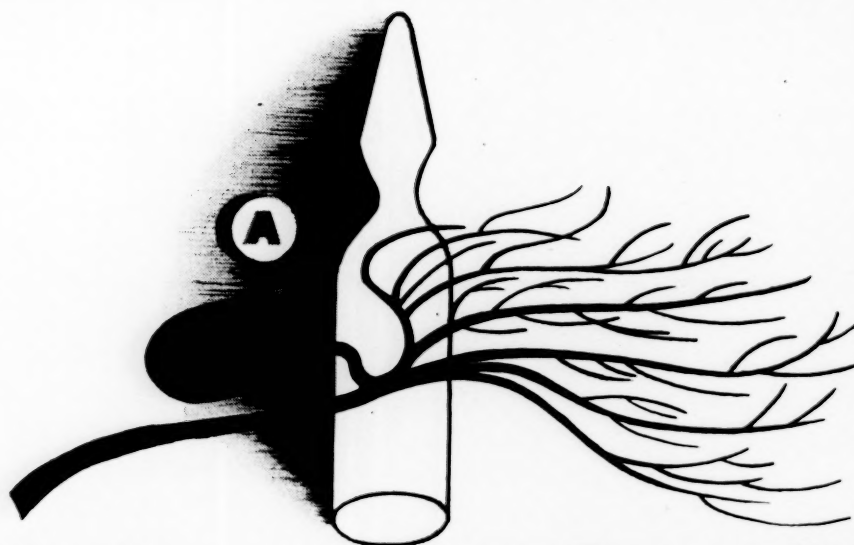
- Rheumatoid Arthritis in the Aged . RUSSELL L. CECIL AND WILLIAM H. KAMMERER 439

Analysis of 100 cases of rheumatoid arthritis with onset after the age of sixty revealed few significant differences from the disease picture in younger persons.

- The L. E. (Lupus Erythematosus) Cell. Clinical and Chemical Studies
STANLEY L. LEE, SIDNEY R. MICHAEL AND I. LUTFI VURAL 446

The authors throw additional light upon the origin and nature of the L. E. cell which in their experience occurs only in disseminated lupus erythematosus. Evidence is submitted that the inclusion body of the L. E. cell is altered nuclear material derived chiefly from polymorphonuclear leukocytes, that it consists largely of partially depolymerized desoxyribose nucleic acids and is identical with the "hematoxylin-staining body" of Klemperer.

Contents continued on page 5



in biliary tract disorders

Hydrocholeresis with *Decholin* and *Decholin Sodium* produces a gentle lavage of the biliary tree. Copious, fluid bile flushes away mucus, pus and thickened bile and re-establishes normal drainage.

for best results

Hydrocholeretic therapy should be extended through the optimal treatment period. An average dose of *Decholin* is 1 or 2 tablets three times daily for four to six weeks. Prescription of 100 tablets is recommended for maximum efficacy and economy. The course may be repeated after an interval of one or two weeks if desired. For more rapid and intensive hydrocholeresis, therapy may be initiated with *Decholin Sodium*.

DECHOLIN

Decholin tablets (brand of dehydrocholic acid) of 3¾ gr. (0.25 Gm.), in bottles of 100, 500, 1,000 and 5,000.

Decholin Sodium (brand of sodium dehydrocholate) is supplied in a 20% solution for intravenous administration. 3 cc., 5 cc. and 10 cc. ampuls — boxes of 3, 20 and 100.

Decholin and *Decholin Sodium*, trademarks reg.

AMES COMPANY, INC • ELKHART, INDIANA

Ames Company of Canada, Ltd., Toronto



C O N T E N T S

The American Journal of Medicine

VOL. X APRIL, 1951 No. 4

Contents continued from page 3

Treatment of Leukemia with Aminopterin . LEO M. MEYER AND ABBOTT NEWMAN 452

Contrary to earlier enthusiastic reports aminopterin was not found to effect improvement in acute leukemia.

The Continuing Hazard of Bromide Intoxication

HORACE H. HODGES AND MONROE T. GILMOUR 459

The authors speak plainly about the continuing unnecessarily high incidence of bromide intoxication in some areas and what should be done about it.

Criteria for the Management of Neurosyphilis

BERNHARD DATTFNER, EVAN W. THOMAS AND LOPO DE MELLO 463

The authors draw from a large experience to give a number of practical pointers in the choice and interpretation of spinal fluid tests for management of neurosyphilis.

Review

Newer Concepts of the Role of Sodium in Disease T. S. DANOWSKI 468

This timely review summarizes current views regarding factors regulating sodium concentration in extracellular fluid, the significance of decreased and increased sodium levels, possible relation of sodium to vascular disease and the movement of sodium in and out of cells.

Seminars on Pulmonary Physiology

Physiopathologic Aspects of Chronic Pulmonary Emphysema

JOHN R. WEST, ELEANOR DEF. BALDWIN, ANDRÉ Cournand and

DICKINSON W. RICHARDS, JR. 481

This important contribution summarizes and integrates the results of many years of investigation of pulmonary function in chronic pulmonary emphysema. Data on lung volume, mechanics of respiration, pulmonary gas exchange and the nervous regulation of ventilation are presented, with special emphasis on the significance of inadequate alveolar ventilation. Four more or less distinct patterns of pulmonary insufficiency are described, with illustrative cases. On the basis of these new concepts problems of management are reconsidered.

Contents continued on page 7

Anxiety and Autonomic Lability as the Basis of Functional Disorders

Emotional response to the stress of life is the primary source of illness in a steadily increasing number of cases. *Weiss* and *English*¹ estimate that as high as two-thirds of all patients have disorders due either entirely or in part to emotional factors and anxiety. *Ebaugh*² refers to anxiety as "... the universal disease of our times".

Complete examination discloses no organic basis for the symptoms in these cases, yet the clinical picture may mimic a true organic disease.

The symptom-complex usually involves several or-

gan systems.^{2,3,4} In such cases, the anxiety is channeled into organ dysfunction via the autonomic nervous system.^{2,3,5,6} Some of the effects produced by exaggerated activity of a labile autonomic system are tabulated below. Many of these, it will be noted, are related to the symptoms which feature prominently in functional disorders. The symptoms in any one case are not necessarily limited to one organ system. Usually some are referable to sympathetic hypertonicity, others to parasympathetic hypertonicity.

ORGAN SYSTEM	SYMPATHETIC HYPER- TONICITY	PARASYM- PATHETIC HYPER- TONICITY	SYMPTOMS OF FUNCTIONAL DISORDER	AUTONOMIC LABILITY
GASTRO- INTESTINAL	Hypomotility Hyposecretion Intestinal Atony	Increased Salivation Hypermotility Hypersecretion	Belching Heartburn Nausea & vomiting Mucous diarrhea	When a patient exhibits a clinical picture suggestive of non-organic dysfunction, the diagnosis of Functional Disorder can be facilitated by use of the following indications of Autonomic Lability: Variable Blood Pressure Temperature Variations Changing Pulse Rate Deviations in B.M.R. Exaggerated Cold Pressure Reflex Oculo-cardiac Reflex Abnormalities Glucose Tolerance Alterations
CARDIO- VASCULAR	Rapid heart rate Peripheral vaso- constriction Slight rise in blood pressure	Reduced heart rate Vasodilatation Lowered blood pressure	Palpitation Sinus tachycardia Premature systoles B.P. low in some; elevated in others	
RESPIRATORY	Dry nasopharyngeal mucous membrane Bronchial relaxation	Increased nasopharyngeal secretion Bronchial constriction Laryngospasm	Dry mouth and throat Difficulty in breathing Sighing respiration	
GENITO- URINARY	Bladder detrusor relaxed; Sphincter contracted Ureter tone and motility decreased	Bladder detrusor contracted; Sphincter relaxed Ureter tone and motility increased	Urinary frequency Difficulty in urinating Dysmenorrhea Menstrual irregularity	

This tabulation is based on data available in references 1 to 6 stated below.

Primarily, the patient visits his physician out of concern over his symptoms. At this point, he is either unaware of his basic emotional problem or ignores it. A complete examination will rule out organic disease and thus reassure the patient. Then, treatment is directed along two lines: First, relieve the patient of subjective distress by drug therapy.* He will then be more cooperative in discussing his emotional problems. Then, having uncovered the basic problem, guidance is given toward correcting

unhealthy situations and attitudes.

*The fact that autonomic dysfunction plays a large part in mediating the disturbance suggests autonomic sedation. A number of independent studies indicate that this therapeutic approach is effective.^{7,8,9} The investigators used ergotamine tartrate (adrenergic blockade), levo-alkaloids of belladonna (cholinergic blockade) and phenobarbital (central sedation) in the form of *Bellergal* tablets. The total effect is an integrated sedation of the entire A.N.S.

1. WEISS, E., and ENGLISH, O.: *Psychosomatic Medicine*, ed. 2, Saunders Co., 1949.
2. EBAUGH, F. G.: *Postgrad. Med.* 4: 208, 1948.
3. WILLIAMS, E. Y., et al: *J. Nat. M. A.* 42: 32, 1950.
4. WOOLEY, L.: *South. Med. & Surg.* 102: 157, 1940.
5. KATZ, L. N., et al: *Ann. Int. Med.* 27: 261, 1947.
6. KROGER, W. S., et al: *Am. J. Obst. & Gynec.* 59: 328, 1950.
7. KARNOSH, L. J., and ZUCKER, E. M.: *A Handbook Of Psychiatry*, Mosby Co., 1945.
8. HARRIS, L. J.: *Canad. M. A. J.* 58: 251, 1948.
9. SLAGLE, G. W.: *J. Michigan M. Soc.* 47: 119, 1942.

**Sandoz
Pharmaceuticals**

DIVISION OF SANDOZ CHEMICAL WORKS, INC.
68 CHARLTON STREET, NEW YORK 14, NEW YORK

C O N T E N T S

The American Journal of Medicine

Vol. X APRIL, 1951 No. 4

*Contents continued from page 5**Conference on Therapy*

Management of Thyrotoxicosis 497

Conferences on Therapy (Cornell University Medical College)—This conference brings together critical medical and surgical points of view in the current management of hyperthyroidism in an effort to arrive at a balanced judgment of the usefulness and limitations of the several forms of therapy now available. Among the therapeutic agents evaluated are radioiodine, surgical intervention and propylthiouracil.

Clinico-pathologic Conference

Recurrent Syncope 506

Clinico-pathologic Conference (Washington University School of Medicine)—This case presents a problem of general interest, the consequences of arteriosclerosis in elderly subjects. In this instance the chief clinical manifestation of arteriosclerosis was recurrent syncope.

Special Feature

American Federation for Clinical Research—Abstracts of Papers Presented at the Eighth Annual Meeting of the Midwestern Section in Chicago, November 2, 1950 513

*Case Reports*Lymphocytic Leukemoid Reaction Associated with Primary Carcinoma of the Breast
CHARLES R. KLEEMAN 522

Lymphocytic leukemoid reactions occur rarely in neoplastic disease, a well documented case being described here.

Sickle Cell Anemia Simulating Poliomyelitis in a White Adult
ROBERT S. GORDON AND HORACE T. GARDNER 528

A difficult and instructive problem in differential diagnosis is discussed in this article.

Change of address must reach us one month preceding month of issue.



From a Single Dose...

8 to 24 hours of Allergy Relief

In the rapidly-expanding file of clinical reports on antihistaminic drugs, this important conclusion appears with greater and greater frequency: DI-PARALENE Hydrochloride (Chlorcyclizine Hydrochloride, Abbott) provides *prolonged allergy relief* with a low incidence of side-effects.

DI-PARALENE is not just another antihistaminic. It is new and different, with a piperazine side chain rather than one of the conventional type. In many cases relief up to 24 hours can be obtained from a single dose. In starting treatment, DI-PARALENE should be administered in 50-mg. doses three times a day for the average adult, but in the majority of cases this dosage can later be reduced to one or two doses a day. One dose taken at bedtime often provides symptomatic relief throughout the night. Often no additional dosage is required until the next bedtime.

Try longer-acting DI-PARALENE in your allergy cases this season. It's available at your prescription pharmacy in 50-mg. and 25-mg. tablets in bottles of 100 and 500.

Abbott

Specify Abbott's new long-acting antihistaminic

DI-PARALENE *hydrochloride*

TRADE MARK

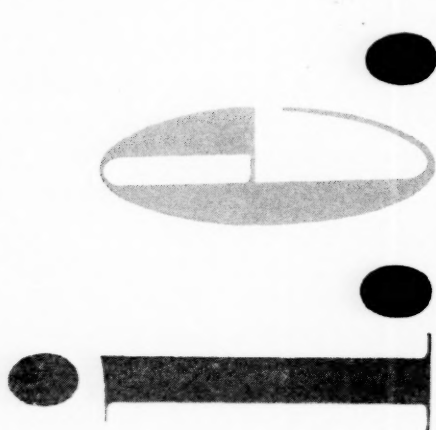
(CHLORCYCLIZINE HYDROCHLORIDE, ABBOTT)

REFERENCES: Spielman, A. D. (1950), N.Y. St. J. Med., 50:2297, Oct. 1. Brown, E. A., et al. (1950), Ann. Allergy, 8:32, Jan.-Feb. Jenkins, C. M. (1950), J. Nat. Med. Assn., 42:293, Sept. Cullick, Louis, and Ogden, H. D. (1950), South. Med. J., 43:632, July. Ehrlich, N. J., Kaplan, M. A. (1950), Ann. Allergy, 8:682, Sept. - Oct.

**"PREMARIN"
WITH
METHYLTESTOSTERONE**

i.e.

wherever combined estrogen-androgen therapy is indicated



i.e. in fractures and osteoporosis in either sex to promote bone development, tissue growth, and repair.

i.e. in the female climacteric in certain selected cases.

i.e. in dysmenorrhea in an attempt to suppress ovulation on the basis that anovulatory bleeding is usually painless.

i.e. in the male climacteric to reduce follicle-stimulating hormone levels.

"Premarin" with Methyltestosterone

for combined estrogen-androgen
therapy

A steroid combination which permits utilization of both the complementary and the neutralizing effects of estrogen and androgen when administered concomitantly. Thus certain properties of either sex hormone may be employed in the opposite sex with a minimum of side effects.

Availability: Each tablet provides estrogens in their naturally occurring, water-soluble, conjugated form expressed as sodium estrone sulfate, together with methyltestosterone.

No. 879—Conjugated estrogens equine ("Premarin").....1.25 mg.
Methyltestosterone10.0 mg.
Bottles of 100 tablets (yellow)

No. 878—Conjugated estrogens equine ("Premarin").....0.625 mg.
Methyltestosterone5.0 mg.
Bottles of 100 tablets (red)



Ayerst, McKenna & Harrison Limited
22 East 40th Street, New York 16, N. Y.

*NEW high dosage
liquid concentrate for
greater convenience
and flexibility in therapy*

CRYSTALLINE
Terramycin
HYDROCHLORIDE

ORAL DROPS

*the only broad-spectrum antibiotic
available in drop-dose potency*

provides: 200 mg. of Crystalline Terramycin Hydrochloride per cc.; approximately 50 mg. in each 9 drops.

plus appeal of attractive cherry color and pleasing cherry-mint flavor.

readily miscible with most foods, milk and fruit juices



affords ease and simplicity of administration
and permits a further simplification of dosage schedules in mild and severe infections, and with patients of all age and weight levels.

Available at prescription pharmacies in 10 cc. bottles with specially calibrated dropper.

Antibiotic Division

Pfizer

CHAS. PFIZER & CO., INC., Brooklyn 6, N. Y.

1941 • A DECADE OF PROGRESS IN ANTIBIOTIC THERAPY • 1951



SAFETY FIRST

Neohetramine is available as:



Tablets Neohetramine,
25 mg., bottles of
100 and 1000.
50 mg., bottles of
100 and 1000.
100 mg., bottles of
100 and 1000.

Syrup Neohetramine,
pint and gallon bottles,
6.25 mg. per cc.

Cream Neohetramine,
2%, 1 oz. tubes.

.. in antihistamine therapy



Every careful physician will ask about an antihistamine: "How safe is it?" Which drug, useful as an antihistaminic and clinically safe, should be a prescription of choice? • Numerous reports suggest the answer: *Neohetramine, in therapeutic doses, is one of the best tolerated of the antihistamines.*^{1,3,4} Both the incidence and degree of side effects are low;^{2,5} and the drug may often be employed in cases intolerant to other antihistamines.⁴ Yet the usefulness of Neohetramine is clinically equivalent to that of other preparations. • Prescribe Neohetramine, for "safety first", when antihistamine therapy is indicated. Professional samples will be sent upon request.

*"... and the drug
may often be employed
in cases intolerant to
other antihistamines"*

Dosage: Average individual dose is 50 to 100 mg., 2 to 4 times daily.
Children, 25 mg., 2 to 4 times daily.

References: 1. Alexander, H. L.: Postgrad. Med. 3:278 (April) 1948. 2. Bernstein, J. B., and Feinberg, S. M.: J. Allergy 19:393 (Nov.) 1948. 3. Crip, L., and Aaron, T. H.: J. Allergy 19:215 (July) 1948. 4. Friedlaender, S. M., and Friedlaender, A. S.: J. Lab. & Clin. Med. 33:865 (July) 1948. 5. Schwartz, E.: Ann. Allergy 5:770 (Nov.-Dec.) 1949.

NEPERA CHEMICAL CO., INC., YONKERS, N. Y.

Neohetramine[®]

HYDROCHLORIDE



Brand of Thonzylamine Hydrochloride, N, N dimethyl-N'p-methoxybenzyl-N'(2-pyrimidyl) ethylenediamine monohydrochloride.

for effectiveness... for tolerance... in antihistaminic therapy

Neohetramine is marketed exclusively to physicians. It is an original and exclusive development of Nepera Chemical Co., Inc.—an organization devoted to research and manufacture of fine pharmaceutical products.

Patient Carries on Normal Pursuits

Throughout the course of treatment for urinary disorders many patients continue their usual activities, thanks to analgesia produced with orally administered Pyridium.

Pyridium can be safely administered concomitantly with antibiotics, the sulfonamides, and other specific therapy.

An analysis of symptomatic relief in 118 cases treated with Pyridium shows:*

Urinary frequency promptly relieved in 85% of cases.

Pain and burning decreased in 93% of cases.

*Kirwin, T. J., Lowsley, O. S., and Manning, J.: Effects of Pyridium in certain urogenital infections, *Am. J. Surg.* 62: 330-335, December 1943.

The complete story of Pyridium and its clinical uses is available on request.

THROUGH GRATIFYING RELIEF

*of the symptoms of
urinary tract
infection*



PYRIDIUM®

(Brand of Phenylazo-diamino-pyridine HCl)

Pyridium is the trade-mark of Nepera Chemical Co., Inc., successor to Pyridium Corporation, for its brand of phenylazo-diamino-pyridine HCl. Merck & Co., Inc. sole distributor in the United States.

MERCK & CO., INC.

Manufacturing Chemists

RAHWAY, NEW JERSEY

In Canada: MERCK & CO. Limited—Montreal

For **go-between...**

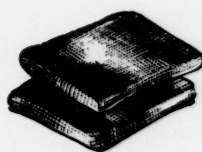
OXYCEL[®]

(OXIDIZED CELLULOSE)

In the control of bleeding between arterial and venous systems, where vessel size precludes the use of hemostat and suture, OXYCEL—absorbable hemostatic—provides prompt control of capillary bleeding. Trauma is minimized, operative procedures shortened, and post-operative hemorrhage notably curtailed. OXYCEL is practical and convenient, too... applied direct from the container, it conforms readily to all wound surfaces.

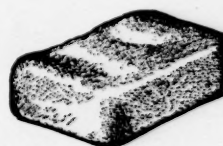
Package Information:

Supplied in individual glass containers in the following convenient forms:



OXYCEL PADS:

Sterile, gauze-type, 3 inch x 3 inch eight-ply pads, and 4 inch x 12 inch eight-ply pads.



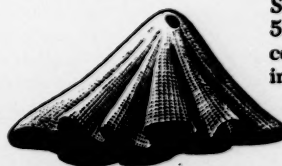
OXYCEL PLEDGETS:

Sterile, cotton-type 2¼ inch x 1 inch x 1 inch portions.



OXYCEL STRIPS:

Sterile, four-ply gauze-type strips 18 inch x 2 inch; four-ply, 5 inch x ½ inch; and four-ply 36 inch x ½ inch, pleated in accordion fashion.



OXYCEL FOLEY CONES:

Sterile, four-ply, gauze-type discs, 5 inch and 7 inch diameters, conveniently folded in radially fluted form.



PARKE, DAVIS & COMPANY

BOOK SECTION

"We have not read an author till we have seen
his object, whatever it may be, as he saw it."

—Carlyle

Another MOSBY BOOK!

NEW FOURTH EDITION—BRAY'S

CLINICAL LABORATORY METHODS

616 pages

119 illustrations

(18 in color)

Price, \$7.25

With great pleasure we announce publication of the Fourth Edition of this well-known and popular book by Dr. Bray. First published in 1936, it has been enthusiastically received in each succeeding edition because of its compactness and for its easily accessible information on most frequently used laboratory tests and their interpretation.

The new edition includes considerable new material—new illustrations and charts—new tests dealing

with intestinal parasites, the importance of which is increased because of our closer contact with the tropics. There are so many new tests included in this Fourth Edition that space does not permit their listing here.

It continues to stress the clinical significance of laboratory findings, making it an extremely helpful guide in diagnosis for the internist and for the medical student in any branch of clinical medicine.

By W. E. BRAY, B.A., M.D., Professor of Clinical Pathology, University of Virginia. Director of Clinical Laboratories, University of Virginia Hospital.

The Mosby Company Has Bookdealers in Leading Cities Throughout the World.

The C. V. MOSBY Company

Scientific Publications

3207 Washington Blvd.

St. Louis 3, Missouri



Now! Clinical Use of ACTH

*Proceedings
of the 2nd
Clinical ACTH
Conference*

Edited by
Dr. John R. Mote
Volume I. Research
Volume II. Therapeutics

No where else can the busy practitioner find all the latest information on the clinical use of ACTH.

This new book—in two volumes—contains all that was reported and discussed at the second clinical ACTH conference held recently in Chicago.

Since ACTH is now available for use in daily practice, this book—containing *both the basic and clinical aspects* of the subject—should be within reaching distance of every practitioner's desk.

In Two Volumes—Publication Date, May 9

Volume I. New Basic Research

- I. General Adrenal Cortical Physiology and Adrenal Cortical Steroid Secretion and Excretion—10 reports and discussions
- II. Kidney and Electrolytes—12 reports and discussions
- III. Nitrogen Metabolism—7 reports and discussions
- IV. Carbohydrates and Fat Metabolism—4 reports and discussions
- V. Vitamin Metabolism—2 reports and discussions
- VI. Adrenal Gland and Hemopoietic System—7 reports and discussions
- VII. Fundamental Acute Inflammatory Reaction: Infection, Immunology and Hypersensitivity—7 reports and discussions

278 Illus., 49 Tables, 566 Pages, \$8.50

Volume II. Clinical Applications

- I. General—4 reports and discussions
- II. Metabolic or Physiologic Defect—8 reports and discussions
- III. Hemopoietic Diseases; Malignancy in General—7 reports and discussions
- IV. Surgical Use—6 reports and discussions
- V. Infectious Disease and Liver Disease—4 reports and discussions
- VI. Hypersensitivity—5 reports and discussions
- VII. Toxins and Toxic Materials—2 reports and discussions
- VIII. Inflammatory Diseases of Unknown Etiology—7 reports and discussions
- IX. Collagen Disease—10 reports and discussions

316 Illus., 81 Tables, 706 Pages, \$8.50

A limited supply of the *Proceedings of the First Clinical ACTH Conference* containing the basic facts upon which clinical findings are based are still available at the new low price of only \$3.00.

Cardiology Books

EAST: CARDIOVASCULAR
DISEASE IN GENERAL
PRACTICE—3rd Edition

Prepared especially for the general practitioner. Includes coronary occlusion, hypertension, thyrotoxicosis, congenital defects, pulmonary disorders and peripheral failure. 34 Illus.—208 Pages—\$4.00

EAST AND BAIN: RECENT
ADVANCES IN CARDI-
OLOGY—4th Edition

Emphasis is upon treatment and early recognition of disorders. The importance of health and efficiency of heart muscle is the dominant theme and the various lesions and conditions that affect it are fully considered. 98 Illus.—454 Pages—\$6.25

Now in 2nd Printing!

PRINCIPLES OF INTERNAL MEDICINE

edited by Drs. T. R. Harrison, M. M. Wintrobe, Paul B. Beeson, William H. Resnik, and George W. Thorn

"This is an excellent textbook and an important addition to any physician's library. The style of presentation is new and progressive . . . a valuable, important book crammed full of useful information and so styled as to make it easy to dig out."

ARCHIVES OF INTERNAL
MEDICINE

245 Illustrations—1,590
Pages—\$12.00

New!

SPATIAL VECTOR ELECTROCARDIOGRAPHY

Clinical Electrocardiographic Interpretation

by Drs. Robert P. Grant and
E. Harvey Estes

The vexing problem of reading and interpreting electrocardiograms has been greatly simplified in this new text by the use of vector methods. Written in simple and non-technical terms, it is designed for daily use by practitioners and students who have had no special training in physics or mathematics.

It contains only those theoretical aspects absolutely indispensable for a clear understanding of the *clinical* applications of ECG.

The use of vector methods gives simple, accurate and objective interpretations of normalities and abnormalities. When combined with the "pattern" and empirical methods, it makes the interpretation objective rather than intuitive.

The material included covers the ventricular ECG—a discussion of the QRS and T abnormalities.

Ready June

IN CANADA—105 BOND ST., TORONTO 2

The Blakiston Company

1012 Walnut Street
Philadelphia 5, Pa.



Use This Handy Coupon to Order Your Copies Today!

The Blakiston Company, 1012 Walnut Street, Philadelphia 5, Pa.

Please send me the following books. ☐ My check is enclosed; ☐ charge my account. It is understood that you will credit my account in full for any book that I wish to return within 10 days.

- ☐ "Proceedings of the 2nd ACTH Conference" ☐ Volume I. ☐ Volume II.
☐ "Proceedings of the 1st ACTH Conference" ☐ Grant & Estes' "Spatial Vector Electrocardiography"
☐ East's "Cardiovascular Disease in General Practice"—3rd Ed. ☐ East & Bain's "Recent Advances in Cardiology"—4th Ed.
☐ Harrison's "Principles of Internal Medicine"

Name _____
 Address _____
 City _____ Zone _____ State _____

A.J.M. 4-51

NELSON ANNOUNCES

A NEW PRICE POLICY!

The spiral of inflation has probably hit no group harder than the medical profession. Caught between the rising cost of living on one hand, and moderate fees on the other, the doctor has a difficult time just making ends meet. We of Nelson, as publishers to the medical profession, are well aware of this unhappy state of affairs, and we are determined to hold the line, in spite of skyrocketing production costs, to do everything possible to bring good medical books within the reach of every doctor, teacher and medical student in the country . . . regardless of his income.

In line with this we take great pride in announcing the publication of two new books, priced in accordance with our policy of good books at low prices.

Graybiel's CLINICAL ELECTROCARDIOGRAPHY

In this concise guide to the use of electrocardiographic method maximum consideration is given to the use of electrocardiography in every day practice. The 140 illustrations, including some special diagrams of the heart, are clear and crisp with careful attention paid to every detail. This is a book of great practical value to the man in general practice, as well as to the internist and cardiologist.

Ashton Graybiel, M.D., Capt. (MC) USN, Co-ordinator of Research,
U. S. Naval School of Aviation Medicine, Pensacola, Fla.

208 pages

• 140 illustrations •

\$5.00

COMING IN JUNE

Corscaden's GYNECOLOGIC CANCER

In this challenging book Dr. Corscaden places the responsibility for the early detection of gynecologic cancer squarely up to the medical profession. He demonstrates how the cures in gynecologic cancer can be trebled and even quadrupled without the discovery of any new principle or technique in diagnosis or therapy! A book of great importance to every one interested in medicine, whether he be practitioner, specialist, or student.

James A. Corscaden, M.D., Professor Emeritus of Clinical Gynecology,
Columbia University

384 pages

• 110 illustrations •

\$6.00

ORDER THRU YOUR BOOKSTORE OR USE THIS COUPON

THOMAS NELSON & SONS

AJM-451x

19 East 47th St., N. Y. 17

Please send me the following books:

Graybiel's CLINICAL ELECTROCARDIOGRAPHY
Corscaden's GYNECOLOGIC CANCER

\$5.00
6.00

☐ Check enclosed

☐ Send invoice

NAME _____

ADDRESS _____

CITY _____ ZONE _____ STATE _____

liver disorders

diabetes

atherosclerosis

coronary occlusion

hypertension

obesity

nephrosis

methiscol

u.s. vitamin corporation

aqueous natural vitamin A in capsules



A

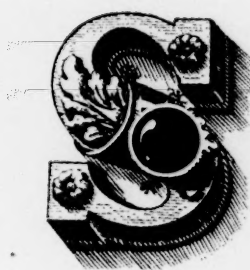
advantages:

up to 400%
greater absorption
80% less excretion
85% higher liver storage

indications:

for more rapid,
more effective therapy
in all vitamin A
deficiencies... particularly
those associated with
conditions characterized
by poor fat absorption
(dysfunction of the
liver, pancreas, biliary
tract and intestines;
celiac and other
diarrheal diseases).

Proven effective in
ACNE and other dermal
lesions responsive to
high potency vitamin A.



ugar-coated for dependable diuresis

Sugar coating is one reason for the superiority of Tablets MERCUHYDRIN with Ascorbic Acid.

Maximum absorption of mercury occurs in the stomach and duodenum—too high for enteric-coated tablets. But poorly tolerated oral mercurials *must be* enteric-coated. Only well-tolerated Tablets MERCUHYDRIN with Ascorbic Acid can be sugar-coated . . . give consistently greater diuresis with less mercury.

For dependable diuresis and minimal side effects prescribe

tablets

MERCUHYDRIN[®]

with ascorbic acid

The simplest method of outpatient maintenance

dosage: One or two tablets daily, morning or evening, preferably after meals.

available: Bottles of 100 simple sugar-coated tablets each containing meralluride 60 mg. (equivalent to 19.5 mg. of mercury) and ascorbic acid 100 mg.

To secure the greatest efficacy and all the advantages of Tablets MERCUHYDRIN with Ascorbic Acid, prescribe a three-week initial supply . . . 25 to 50 tablets.

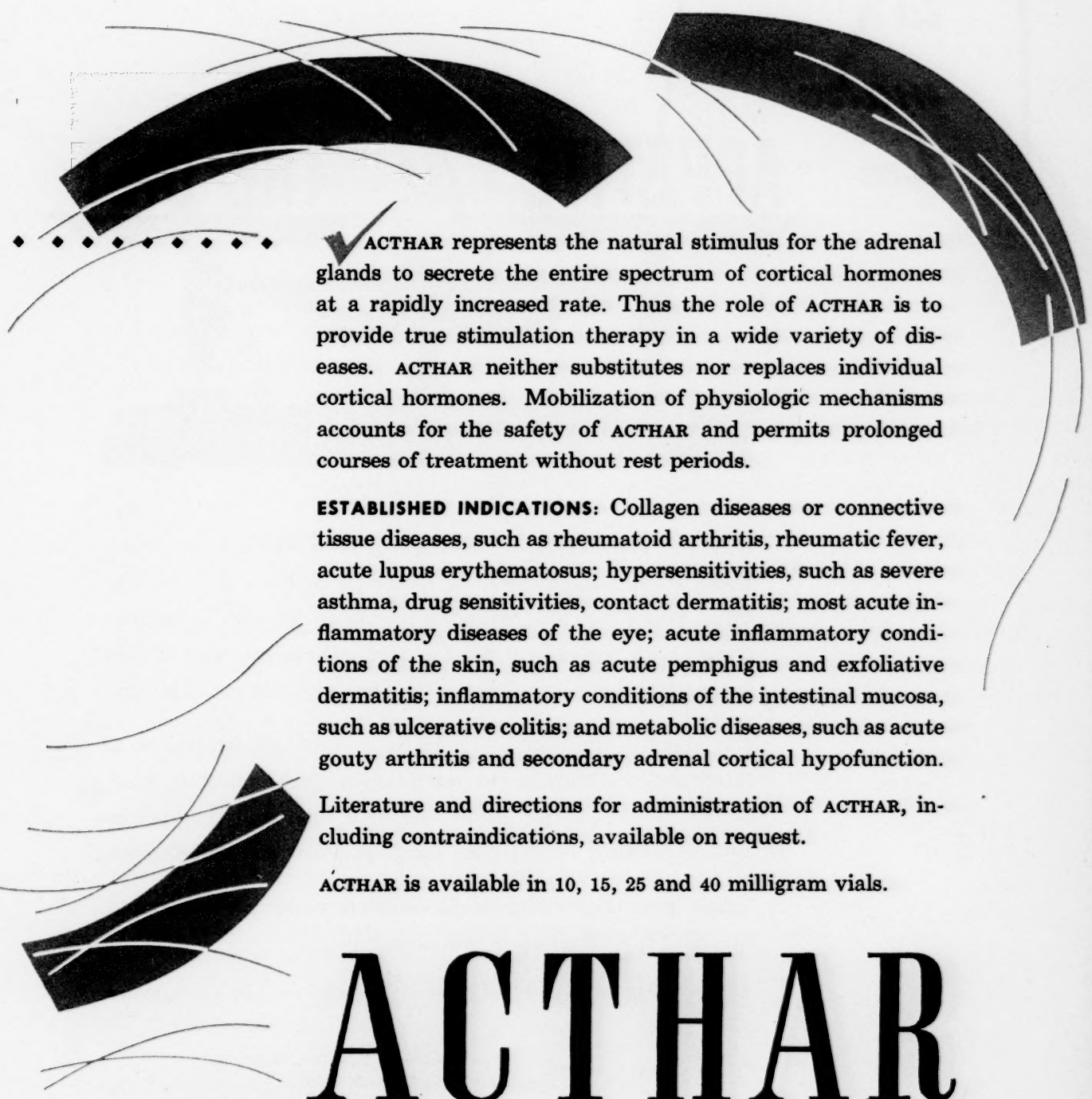
M-15

*L*akeside
laboratories, INC., MILWAUKEE 1, WISCONSIN

TRUE STIMULANT THERAPY...

ADRENAL CORTEX





✓ ACTHAR represents the natural stimulus for the adrenal glands to secrete the entire spectrum of cortical hormones at a rapidly increased rate. Thus the role of ACTHAR is to provide true stimulation therapy in a wide variety of diseases. ACTHAR neither substitutes nor replaces individual cortical hormones. Mobilization of physiologic mechanisms accounts for the safety of ACTHAR and permits prolonged courses of treatment without rest periods.

ESTABLISHED INDICATIONS: Collagen diseases or connective tissue diseases, such as rheumatoid arthritis, rheumatic fever, acute lupus erythematosus; hypersensitivities, such as severe asthma, drug sensitivities, contact dermatitis; most acute inflammatory diseases of the eye; acute inflammatory conditions of the skin, such as acute pemphigus and exfoliative dermatitis; inflammatory conditions of the intestinal mucosa, such as ulcerative colitis; and metabolic diseases, such as acute gouty arthritis and secondary adrenal cortical hypofunction.

Literature and directions for administration of ACTHAR, including contraindications, available on request.

ACTHAR is available in 10, 15, 25 and 40 milligram vials.

ACTHAR



ARMOUR LABORATORIES BRAND OF ADRENOCORTICOTROPIC HORMONE (A. C. T. H.)

THE ARMOUR LABORATORIES

CHICAGO 11, ILLINOIS

PHYSIOLOGIC THERAPEUTICS THROUGH BIORESEARCH

to
make
the

APPETITE *fit* **THE DIET**



It is well known that the craving for food which besets many obese people cannot easily be controlled by the will alone. For them, adherence to a reducing diet often imposes a nervous strain, with consequent tension and irritability; and if they succumb to their urge to eat more, they have a sense of failure.

But appetite can now be modified by oral administration of 'Methedrine'. Then avoidance of over-eating becomes practically effortless, and the patient feels fitter and cheerful, as well as satisfied . . . with his meals and with his achievement.

Trials have shown that 'Methedrine' is a reliable anorexiant, and that it is effective in low dosage.

Literature describing dosage and recommended regimen will be sent on request.

REFERENCES:

Ray, H. M.: *Am. J. Digest. Dis.*, 14:153, 1947.
Shapiro, S.: *ibid*, 14:261, 1947.

'METHEDRINE'®

brand

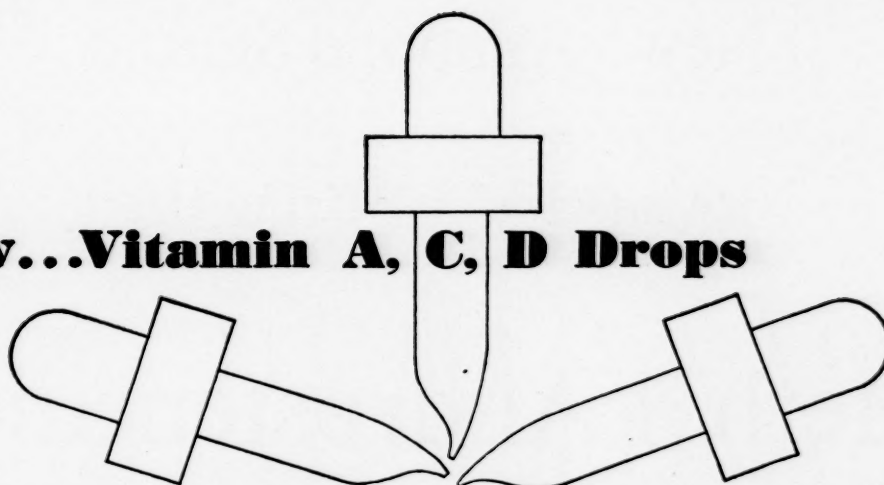
Methamphetamine Hydrochloride (d-Desoxyephedrine Hydrochloride)

Compressed products of 5 mg.—Scored to facilitate division.



BURROUGHS WELLCOME & CO. (U.S.A.) INC. TUCKAHOE 7, NEW YORK

Now...Vitamin A, C, D Drops



in aqueous solution  **for better absorption**

Aquasperse

Vitamin ACD Drops

Advantages:

Aqueous Solution—means faster and more efficient absorption of the fat-soluble vitamins A and D.

In conditions in which fat absorption is impaired, such as diarrheas, celiac disease, hepatic and biliary disturbances, the value of an aqueous solution is obvious.

Hypoallergenic—all the component vitamins of Aquasperse are synthetic. Consequently it may be used where patients cannot tolerate natural source vitamins.

Pleasant flavor...no objectionable odor—Aquasperse has an appealing, slightly citrus flavor and practically no odor.

EACH 0.6 CC. CONTAINS:

vitamin A.....	5000 U.S.P. Units
vitamin D ₃	1000 U.S.P. Units
ascorbic acid.....	50 mg.

Note: The vitamin D₃ in Aquasperse is chemically identical and biologically equivalent to the vitamin D of cod liver oil.

Available—In bottles of 15 cc. and 50 cc. (with calibrated dropper)

WHITE LABORATORIES, INC., Pharmaceutical Manufacturers, Newark 7, N. J.

New Anabolic Steroid

with minimal virilizing effect

Methyl Androstenediol

NOW AVAILABLE FOR CLINICAL RESEARCH

Marked stimulation of protein anabolism, with minimal androgenic effect, has been reported by several investigators of methyl androstenediol.^{1,2,3} • Although definite therapeutic claims are not possible at this time, preliminary results strongly indicate that methyl androstenediol is worthy of clinical trial in those patients in whom nitrogen retention is desired with a minimum of virilizing effect. • Encouraging results in preliminary trials also show that methyl androstenediol may be of value in such gynecological disorders as dysmenorrhea, premenstrual tension, and the menopausal syndrome including osteo-

porosis. • To those qualified investigators interested in further study of this drug, methyl androstenediol is available from Ciba as an *aqueous suspension*, 50 mg. per cc. in 10 cc. vials, for intramuscular use, as *Linguets*, each containing 20 mg., for sublingual use, and as *scored tablets*, each containing 50 mg., for oral use. • Address correspondence to the Division of Clinical Research, Ciba Pharmaceutical Products, Inc., Summit, N. J.

1. Kochakian, C. D.: *Am. J. Physiol.* 158:51, 1949.

2. Gordan, G. S. et al: *Address to Association for the Study of Internal Secretion*, (June 23) 1950.

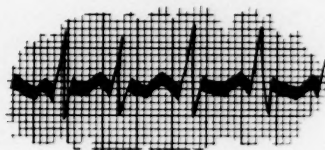
3. Homburger, F., Kasdon, S. C., and Fishman, W. H.: *Proc. Soc. Exper. Biol. and Med.* 74:162, 1950. 2/16694

Ciba PHARMACEUTICAL PRODUCTS, INC., SUMMIT, N. J.

Effective against many bacterial
and rickettsial infections, as well as certain protozoal
and large viral diseases.

AUREOMYCIN

Hydrochloride Crystalline



The Internist today is less
concerned than in former years over cases of pneumonia.
Once highly fatal, this disease has been all but conquered by
modern chemotherapy. For many pneumonias—bacterial,
rickettsial or viral—aureomycin is often a preferred drug.

Packages

Capsules: Bottles of 25 and 100, 50 mg. each capsule. Bottles of 16 and 100, 250 mg. each capsule.
Ophthalmic: Vials of 25 mg. with dropper; solution prepared by adding 5 cc. of distilled water.

LEDERLE LABORATORIES DIVISION

AMERICAN Cyanamid COMPANY

30 Rockefeller Plaza, New York 20, N. Y.

To banish
depression and
nervousness



'Benzebar'—S.K.F.'s logical combination of 'Benzedrine' Sulfate and phenobarbital—ordinarily will dispel the mental depression and relieve the anxiety and tension that accompany so many of life's situations.

These occur, for example, *in association with* . . . family and financial troubles, chronic organic disease, persistent pain, old age and grief; *or following* . . . acute infectious disease, surgical operations, onset of the menopause and childbirth.

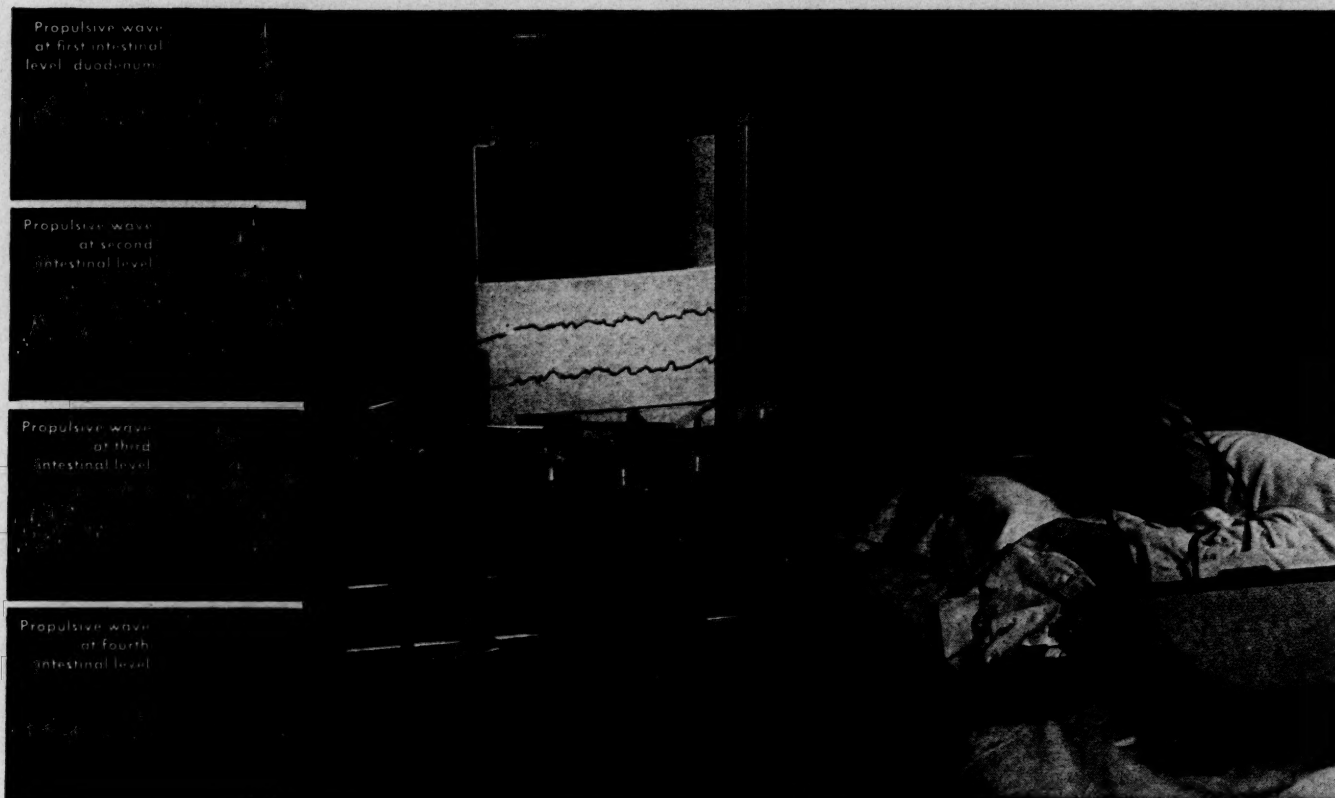
Smith, Kline & French Laboratories, Philadelphia

Benzebar* *the unique antidepressant*

action of 'Benzedrine' Sulfate and the mild sedation of phenobarbital*

Each 'Benzebar' tablet contains 'Benzedrine' Sulfate (racemic amphetamine sulfate, S.K.F.), 5 mg.; phenobarbital, ¼ gr.

*T.M. Reg. U.S. Pat. Off.



Spasmolysis at its Best... by LIVING TEST

Intubation studies^{1,2,3} increasingly confirm the findings of controlled clinical tests and broad professional experience; they dramatically demonstrate the *marked superiority of natural belladonna alkaloids* over the synthetics in relieving smooth muscle spasm.^{2,3}

Donnatal employs precise proportions of the principal alkaloids of belladonna, together with a minimal phenobarbital dosage, to intensify the belladonna effects and help correct emotional factors contributing to the provocation of spasm.

REFERENCES: 1. Chapman, W. P., Rowlands, E. N., and Jones, C. M.: *New England J. Med.*, 243:1, 1950. 2. Kramer, P. and Ingelfinger, F. J.: *Med. Clin. North America*, 32:1227, 1948. 3. Posey, E. L., Barger, J. A., and Dearing, W. H.: *Gastroenterol.*, 11:344, 1948.

FORMULA: Each tablet, each capsule, and each 5 cc. (1 teaspoonful) of Elixir, contains 0.1037 mg. hyoscyamine sulfate, 0.0194 mg. atropine sulfate, 0.0065 mg. hyoscine hydrobromide, and 16.2 mg. (½ gr.) phenobarbital.

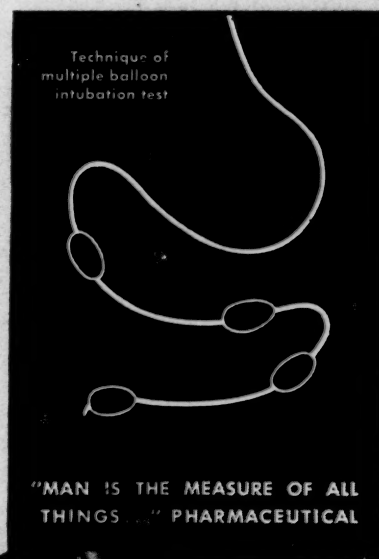
A. H. ROBINS CO., INC., RICHMOND 20, VA.

Donnatal[®]



TABLETS • CAPSULES • ELIXIR

WHENEVER and WHEREVER spasm of smooth muscle causes pain or dysfunction



"MAN IS THE MEASURE OF ALL THINGS" PHARMACEUTICAL



First aid for the "digestive casualty"

Entozyme greatly simplifies a broad therapeutic approach to many often complex disturbances of the gastro-intestinal tract, through its provision of potent amounts of the principal digestive enzymes: pepsin, pancreatin (with its lipase, amylase, and trypsin), and bile. Its special "tablet-within-a-tablet" construction controls the release of each essential digestive enzyme at its own appropriate gastro-enteric level... in its optimal state of enzymatic activity. This unique action explains the relief gratifyingly elicited in so many cases of pathologic or functional impairment of the digestive process.^{1,2,3}

REFERENCES: 1. Kammandel, H. et al.: Bull. N. Y. Med. Coll., Flower & Fifth Ave. Hosps. (in press). 2. McGavack, T. H. and Klotz, S. D.: Bull. N. Y. Med. Coll., Flower & Fifth Ave. Hosps., 9:61, 1946. 3. Weisberg, J. et al.: Am. J. Dig. Dis., 15:332, 1948.

FORMULA: Each tablet contains 300 mg. pancreatin, U.S.P., 250 mg. pepsin N.K., and 150 mg. bile salts.

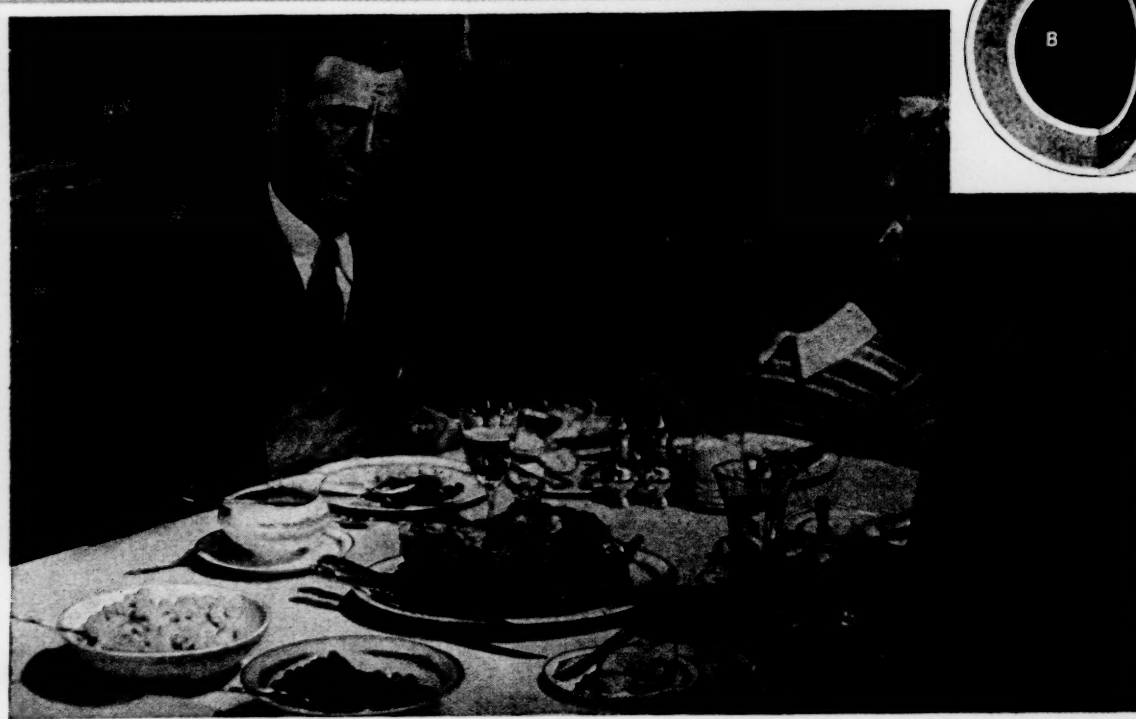
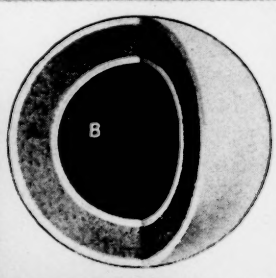
A. H. ROBINS CO., INC., RICHMOND 20, VA.

ENTOZYME®



A SINGULARLY effective, DOUBLE-layered tablet, with TRIPLE-enzyme digestive action.

Gastro-soluble enzymes are released from outer shell (A) in stomach; entero-active enzymes from inner core (B) in duodenum and jejunum.





*Here is the
patient who can
benefit most from*

VERILOID^{*} **IN HYPERTENSION**

The patient with moderate hypertension, who constitutes the great bulk of hypertensives seen clinically, is the one that can benefit most from Veriloid. In his management, dosage is more simple, and the clinical response is as a rule excellent.

By controlling hypertension in its earlier stages, much can be accomplished. Many organic changes directly related to a sustained elevation of blood pressure can be prevented, expanding the years of physical and mental usefulness of the patient.

Veriloid—a distinctive, biologically standardized fraction of *Vera-trum viride*—exerts its well-defined hypotensive action without sacrifice of postural reflexes so important for comfortable living. The average dose of from 2.0 to 5.0 mg. four times daily after meals and at bedtime usually produces a significant, sustained reduction in arterial tension. For optimal results, dosage should be carefully adjusted to the needs and tolerance of the individual patient.

*Trade Mark of Riker Laboratories, Inc.

NOW AVAILABLE IN THREE DOSAGE UNITS

Veriloid is now available in 3 tablet sizes—1 mg., 2 mg., and 3 mg. tablets. The larger tablets are especially useful after dosage needs have been established and are more economical for the patient. Literature available on request.

RIKER LABORATORIES, INC. • 8480 BEVERLY BOULEVARD, LOS ANGELES 48, CALIFORNIA



As a primary dietary
supplement
for the pregnant patient—
there is nothing
better than—

White's **MOL-IRON®**
with **CALCIUM and VITAMIN D**

Mol-Iron—most effective iron therapy known,^{1, 2, 3} now has been supplemented with the essential gestational elements, calcium and phosphorus, in an optimum ratio, plus adequate vitamin D.

The superiority of Mol-Iron as a source of iron is epitomized in the conclusions of Dieckmann:¹ "We have never had other iron salts so efficacious in pregnant patients."

Each easily-swallowed, soft gelatin capsule contains:

Mol-Iron 198 mg.
Dicalcium Phosphate 869 mg.
(anhydrous)
Vitamin D₃ 200 units

Prophylactic Dose: one capsule three times daily after meals.

Therapeutic Dose: two capsules three times daily after meals
(providing 240 mg. Fe++daily).

Supplied: Soft gelatin capsules in bottles of 100.

**ALSO
supplied:**

Mol-Iron Tablets in bottles of 100 and 1000.
Mol-Iron Liquid in bottles of 12 fluid ounces.
Mol-Iron with Liver and Vitamins, capsules, in bottles of 100.

White Laboratories, Inc., Pharmaceutical Manufacturers, Newark 7, N. J.

1. Dieckmann, W. J., and Priddle, H. D.: Am. J. Obstet. & Gynec. 57:541 (1949).

2. Chesley, R. F., and Annitto, J. E.: Bull. Margaret Hague Mat. Hosp. 7:68 (1948).

3. Dieckmann, W. J. et al: Am. J. Obstet. & Gynec. 59:442 (1950).

SPASTIC STATES --

*accompanied by
irritability, tension,
apprehension --*



respond to the antispasmodic action of Pavatrine, combined with the mild central nervous system sedation of Phenobarbital—as exhibited in Pavatrine with Phenobarbital.

Pavatrine is unique in that it exerts two types of spasmolysis—neurotropic and musculotropic—for relief of gastric hypermotil-

ity, cardiospasm, pylorospasm, spasticity of the duodenum including the sphincter of Oddi, bladder spasm and dysmenorrhea.

For the medical management of gall-bladder disease, Pavatrine with Phenobarbital is useful in conjunction with the hydrocholeretic, Ketchol.

PAVATRINE[®] with PHENOBARBITAL

(β -diethylaminoethyl fluorene-9-carboxylate hydrochloride)

RESEARCH IN THE SERVICE OF MEDICINE **SEARLE**



regulate cardiac output...more precisely

Digitaline Nativelle provides *positive maintenance*—positive because it is completely absorbed and uniformly dissipated. It affords full digitalis effect between doses. Since the non-absorbable glycosides, so frequently causing gastric distress, are eliminated, untoward side reactions are rare. Because of this efficiency Digitaline Nativelle is a cardiotonic of choice of leading cardiologists the world over. For the comfort and protection of your patients—for your own assurance—specify Digitaline Nativelle in full when you prescribe.

digitaline nativelle

Send for brochure:
"Modern Digitalis Therapy"
Varick Pharmacal Company, Inc.
(Division of E. Fougera & Co. Inc.)
75 Varick St., New York



Chief active principle of digitalis purpurea (digitoxin)
(not an adventitious mixture of glycosides)

For dosage instructions consult Physicians' Desk Reference



**versatile
hormone
ORETON[®]**
(Testosterone Propionate U.S.P.)

in the male

ORETON supplies androgen to rehabilitate the climacteric or eunuchoid patient.

in the female

ORETON overcomes excessive estrogen activity, and controls functional uterine bleeding and dysmenorrhea. ORETON exerts a palliative effect in carcinoma of the breast.

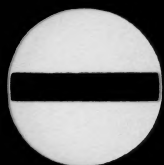
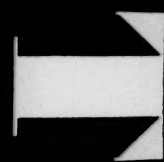
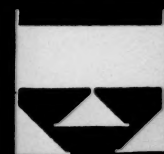
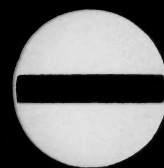
in both sexes

ORETON exhibits a protein anabolic effect, builds tissue and enhances well-being of the aged patient.

ORETON

ORETON, Schering's brand of Testosterone Propionate U.S.P. in oil for intramuscular injection.

Schering CORPORATION • BLOOMFIELD, NEW JERSEY



Meat in the Dietary Regimen in Cirrhosis

Accruing clinical observations clearly indicate that a diet high in complete protein and in the B complex vitamins is a highly successful measure in management of cirrhosis of the liver. Connor states that, prophylactically, a well nourished individual on a diet optimal in protein content and other essentials does not develop cirrhosis.¹

A recent study² again substantiates the finding that proper dietary control improves the prognosis in hepatic cirrhosis. In this study the results from the dietary treatment of 124 patients with cirrhosis of the liver in failure were compared with the results from a control group of 386 patients with hepatic cirrhosis. The severity of the underlying disease process was comparable in both groups.

The dietary regimen of the test group included generous amounts of protein supplemented with vitamin B concentrates; bed rest, diuretics, abstinence from alcohol, and supportive care were also prescribed. Providing about 3,500 calories, the diet contained 140 Gm. of protein, 365 Gm. of carbohydrate, and 175 Gm. of fat. It consisted largely of meat, milk, eggs, fruit, and green vegetables. Yeast or a vitamin B complex preparation was also administered. Thiamine (5 mg., daily) and unconcentrated liver extract (5 cc., twice weekly) were injected intramuscularly. On the other hand, the control group received bed rest, supportive care, and diuretics but no specific die-

tary measures other than a diet high in carbohydrate and low in protein and fat.

As indicated by the statistical results, it was concluded from this study that Laennec's cirrhosis is not necessarily a progressive disease. After several months of treatment clinical improvement was observed in 61 of the 145 patients. Duration of life after onset of ascites was significantly greater than in the control group. At the end of one year, 65 per cent of the treated patients were alive against only 39 per cent of the controls; at the end of two years, 50 per cent of the treated patients and 21 per cent of the controls were alive; and at the end of five years 30 per cent of the treated patients and only 7 per cent of the controls survived. Early diagnosis and treatment, however, should improve the prognosis indicated by these findings.

The value of meat in the dietary control of hepatic cirrhosis is not limited to just its high content of biologically complete protein. Meat also provides valuable amounts of the B vitamins—riboflavin, thiamine, niacin, and the recently discovered vitamin B₁₂.

1. Connor, C. L.: The Etiology and Pathogenesis of Alcoholic Cirrhosis of the Liver, *J.A.M.A.* 112:387 (Feb. 4) 1939.

2. Patek, A. J., Jr.; Post, J.; Ratnoff, O. D.; Mankin, H., and Hillman, R. W.: Dietary Treatment of Cirrhosis of the Liver, *J.A.M.A.* 138:543 (Oct. 23) 1948.

The Seal of Acceptance denotes that the nutritional statements made in this advertisement are acceptable to the Council on Foods and Nutrition of the American Medical Association.



A m e r i c a n M e a t I n s t i t u t e
Main Office, Chicago...Members Throughout the United States

**Wyeth**
®**NEW!****PONDETS** now contain both
PENICILLIN and **BACITRACIN**

The same delicious hard candy, the same color, at no extra cost over the former PONDETS with penicillin alone.

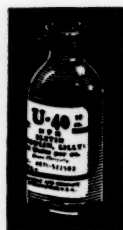
Greater Antibacterial Action, because of penicillin-bacitracin potentiation.

Greater Antibacterial Coverage—Organisms with little or "borderline" sensitivity to either antibiotic become easy prey to this combination.

In each troche—20,000 units penicillin and 50 units bacitracin . . . providing effective oral levels of antibiotic lasting at least one-half hour in most patients.

PONDETS®**PENICILLIN-BACITRACIN TROCHES WYETH***Wyeth* Incorporated, Philadelphia 2, Pa.

simplified



*diabetic management
through
improved time-action
and fewer injections*

NPH ILETIN (INSULIN, LILLY)

For many diabetics taking two or more daily injections of other Insulin preparations, one daily injection of NPH Insulin will often be adequate for purposes of control. This improvement is a long stride toward a more nearly normal life.

For physicians, this development eliminates some of the obstacles which earlier stood in the way of satisfactory adjustment of doses to the patient's needs.

NPH ILETIN (INSULIN, LILLY)

Detailed information and literature concerning NPH Iletin (Insulin, Lilly) are personally supplied by your Lilly medical service representative or may be obtained by writing to



ELI LILLY AND COMPANY • INDIANAPOLIS 6, INDIANA, U. S. A.

Editorial

Collagen Disease*

THE term collagen disease was originally proposed to call attention to systemic alterations of the extracellular components of the connective tissue as a pathologic-anatomic feature common to a group of apparently heterogeneous diseases. It was not intended to use the term in a diagnostic sense since it was realized that it referred to one morphologic characteristic only and therefore obviously could not define the underlying morbid processes of the diseases grouped together. But it was hoped that information regarding the pathogenesis of such obscure maladies as acute lupus erythematosus, diffuse scleroderma and dermatomyositis might be advanced by a rational inquiry into the mechanism of the basic connective tissue alteration.

Klinge had first recognized the significance of systemic alterations of the intermediate substances of the connective tissue for the pathologic-anatomic definition of rheumatic fever and rheumatoid arthritis. He was not the first observer of fibrinoid connective tissue damage and myxomatous swelling of the ground substance in these diseases, but he was the first to recognize that these alterations were of significance for an understanding of the pathogenesis of these maladies. The occurrence of similar changes in hypersensitive rabbits led him to the conclusion that the tissue damage in human rheumatic disease was also due to

hypersensitivity. In consequence he maintained that the same pathogenetic principle operates in other disease entities anatomically characterized by fibrinoid connective tissue damage. This thesis has found wide acceptance. We did not deny the role of hypersensitivity in some of the diseases with systemic implication of the connective tissue, but we did not agree with the sweeping generalization. We also believed that the alterations of the intermediate substances deserved utmost attention and required dynamic interpretation, but we recognized that an explanation in terms of biology must rest upon adequate information regarding their constitution and reactivity.

Ten years ago such information was less than fragmentary. In recent years great advances have been made by the fundamental sciences. The ultrastructure of the collagen fibers has been revealed by the investigations¹ of Schmitt¹ and Gross in this country and Wolpers¹ in Germany. The chemical constitution and the influence of specific enzymes upon the mucopolysaccharides of the homogenous ground substance has been successfully explored by Meyer and others. Investigations by Ludwig, Boas and Soffer point to the role hormones play in the formation of the homogenous ground substance while experiments by Sprunt and McDearmon and by Seifter and associates demonstrate the influence of hormones upon the interaction

* Most of the articles whose authors have been quoted were listed in a recent publication: KLEMPERER, P. Concept of collagen diseases. *Am. J. Path.*, 26: 505-519, 1950.

¹ WOLPERS, C. Die Querstreifung der kollagenen Bindegewebesfibrille. *Virchows Arch. f. path. Anat.*, 312: 292-302, 1944.

between mucopolysaccharides and hyaluronidase. Histologic investigations have been advanced by the application of new methods of histochemistry and Gersh and Catchpole have pointed out that changes in the polymerization of the glycoproteins of the ground substance can be revealed by these technics.

Yet in spite of these brilliant explorations many of the fundamental problems regarding the constitution and physiology of the intermediate substances are still shrouded in mystery. Although the carbohydrate component of the homogenous ground substance has been adequately investigated, the constitution of the protein moiety is hardly known. The mode of fiber formation and its relation to the homogenous ground substance is still obscure although the investigations of Porter and Vanamee on tissue culture begin to throw light on the complexity of the process. One of the problems which is still under scrutiny is the relation of the fibroblast to the formation of the intermediate substances. Today it is generally accepted that the fibroblast does not directly manufacture the collagen fiber but it is widely assumed that the ground substance is an immediate product of the activity of the fixed connective tissue cell; yet critical proof of this theory has not yet been brought forward and the alternative hypothesis of Nageotte and others that an intercellular substance is deposited directly as a transudate from the blood and subsequently elaborated into collagen fibers has not received the attention it deserves. According to Rössle² this mechanism acts in an exaggerated manner in pathologic states. It is referred to as serous inflammation and accounts for characteristic connective tissue changes which may lead to organ sclerosis. The frequency of changes in the proteins and amino sugars of the blood in maladies characterized by alterations of the intermediate substances of the connective tissue (Soffer, Levitt and Baehr³)

² RÖSSLE, R. Über die serösen Entzündungen der Organe. *Virchows Arch. f. path. Anat.*, 311: 252-284, 1944.

³ SOFFER, L. J., LEVITT, M. F. and BAEHR, G. Use of

might support the belief in a direct relationship between these two components of the body. The beneficial effect of cortisone and ACTH on the clinical symptoms and the simultaneous correction of the abnormal chemical blood values (Reiner⁴) is also worthy of mention in this connection. It seems that serious consideration should be given to the inter-relationship between blood and intermediate substances of the connective tissue. Even if further studies should prove that they are manufactured by the fibroblasts, the product of cellular activity would obviously also be dependent on the materials supplied by the blood.

Since the question of normal collagen fiber formation is still unanswered, it cannot be surprising that the problem of the abnormal fibrillar masses, commonly referred to as fibrinoid, has hardly been approached; yet fibrinoid connective tissue change is the dominating structural alteration of the maladies grouped together as collagen diseases. Analysis beyond descriptive characterization with the methods of histology meets with great difficulties because fibrinoid can not be well isolated and thus submitted to chemical and physical identification. But identification with the conventional histologic methods is unsatisfactory because an apparent microscopic identify in different disease entities is ambiguous. Recent studies of Altshuler and Angevine have made it probable that fibrinoid is not altered collagen but that it is formed as a precipitate in the ground substance.

A résumé of the present state of our knowledge of the intermediate substances of the connective tissue would be incomplete without a reference to their role in the general economy of life. Obviously they are not only formed to give support to the body as a whole and to bind together organs and cells; their significance in water and

cortisone and adrenocorticotrophic hormone in acute disseminated lupus erythematosus. *Arch. Int. Med.*, 86: 558-573, 1950.

⁴ REINER, M. Effect of cortisone and adrenocorticotropin therapy on serum proteins in disseminated lupus erythematosus. *Proc. Soc. Exper. Biol. & Med.*, 74: 529-531, 1950.

salt metabolism is evident and, as Schade has pointed out, they are important in the regulation of acid-base equilibrium. We therefore can not afford to neglect them as Virchow⁵ did in postulating that the intercellular substances are not the seat of vital activity nor the living centers of the connective tissue.

It might be true that pathologic-anatomists were not aware of the depth of the

⁵ VIRCHOW, R. *Die Cellularpathologie*, p. 44. Berlin, 1871. A. Hirschwald.

problem when they first called attention to the significance of alterations of the intermediate substances of the connective tissue in certain diseases only. But they have led the way and in cooperation with the fundamental sciences we must now write a pathology of the intermediate substances of which the so-called collagen diseases will be only a chapter.

PAUL KLEMPERER, M.D.
Mount Sinai Hospital,
New York, N. Y.

Clinical Studies

Lung Function Studies*

VI. Detection of Uneven Alveolar Ventilation during a Single Breath of Oxygen

JULIUS H. COMROE, JR., M.D. and WARD S. FOWLER, M.D.

Philadelphia, Pennsylvania

EVALUATION of pulmonary function involves measurement and analysis of many factors. One of these is the evenness with which inspired air is distributed among the millions of alveoli in the lungs. Perfectly uniform alveolar ventilation would mean that during inspiration each alveolus would receive at the same time gas of the same chemical composition and of the same volume (in relation to its previous, pre-inspiratory volume) and that this gas would mix almost instantaneously with the functional residual gas in the alveolus. Uneven alveolar ventilation could be due to (1) sequential distribution of inspired air so that gas from the respiratory dead space (with a lower O_2 and higher CO_2 concentration) is drawn preferentially or predominantly into those alveoli that fill early, (2) unequal distribution of gas volumes among the various alveoli, in relation to their pre-inspiratory volume, (3) failure of intra-alveolar mixing (layering of gases in alveoli) or (4) combinations of these.

Since uneven alveolar ventilation exists in many pulmonary diseases and is an important factor contributing to pulmonary disability in several, a rapid and sensitive test for detecting it and estimating its magnitude should be valuable in the diagnosis of pulmonary disease. This is a report of a new method for measuring uneven alveolar ventilation or abnormal intrapulmonary gas distribution.†

† We prefer these terms to intrapulmonary gas mixing since mixing of gases within individual alveoli appears to be relatively unimportant compared with abnormali-

Methods designed to measure evenness of distribution have been reviewed recently by Fowler.⁶ Unfortunately, those methods which are most precise and least objectionable from the theoretical point of view are not ideal for routine clinical use because they are complex and time-consuming. Among these are the methods of Darling, Cournand and Richards,⁵ Bateman¹ and Birath.² These require measurement of some or all of the following: tidal volume, respiratory dead space, functional residual capacity, the concentration of gases in alveolar, or expired gas and the rate of elimination of N_2 from the rest of the body into the lungs during the breathing of O_2 or other gases.

One relatively simple test devised by Cournand et al.⁴ has had widespread clinical acceptance. In this test the patient simply breathes oxygen for seven minutes; at the end of that time he delivers an alveolar gas sample which is analyzed for nitrogen concentration. If the inspired oxygen is distributed uniformly throughout the lung, it will wash alveolar nitrogen out of all parts of the lung uniformly so that at the end of seven minutes there will be very little nitrogen left. If distribution is non-uniform, hypoventilated areas tend to retain much of their nitrogen until it is forced out of them by the final maximal expiration at the end of seven minutes; in such circumstances the nitrogen concentration in this

ties that may arise from uneven distribution on a regional basis.⁷

* From the Department of Physiology and Pharmacology, Graduate School of Medicine, University of Pennsylvania, Philadelphia, Pa. Supported by a research grant from the Commonwealth Fund.

alveolar gas sample will be abnormally high. Cournand et al.⁴ have placed the upper limit of normal at 2.5 per cent nitrogen. However, this test is not merely a measure of the distribution of inspired air; the final alveolar concentration of nitrogen at the end of seven minutes is influenced also by the functional residual capacity (F. R. C.), effective tidal volume and frequency of breathing.^{3,6} This test could be falsely positive as far as the distribution factor is concerned if the F. R. C. were large in relation to the ventilation* or could be falsely negative if the F. R. C. were small in relation to the ventilation. These factors were all appreciated by Cournand et al.⁴ but they and others have found the test clinically useful in the diagnosis of emphysema because in this condition the F. R. C. is increased, tidal volume may be decreased and abnormal distribution usually exists.

The method that we use has certain advantages. It requires only a single breath of O₂ and is relatively uninfluenced by the character of breathing, the frequency, tidal volume or minute volume of respiration, the F. R. C. or the rate of elimination of N₂ from the body.

METHOD

Our method is essentially that described by Fowler.⁷ It differs from that of Roelsen^{14,15} and earlier workers who trapped and analyzed consecutive fractions of an expired gas sample, largely in our use of continuous methods of gas analysis. This has been made possible by the development of two special instruments. One is the Lilly-Hervey nitrogen meter^{11,12} which provides a continuous analysis of N₂ concentration in respired gas. It operates upon the principle of the familiar neon tube. A very small sample of inspired or expired gas is drawn by a vacuum pump through an electrical discharge tube maintained at about 2 mm. Hg pressure; a high voltage applied to this tube causes the

gas to emit radiation. Air glows with a bright pink color, O₂ a very faint green, N₂ a bright orange pink, CO₂ a dim blue and water vapor a rich red. The spectral region of 3,100 to 4,800 Å excludes the emission from O₂ and water vapor and almost all the CO₂ but includes some of the most intense N₂ bands. A light filter selected to isolate this range is inserted between the discharge tube and a photoelectric cell. The output of this cell can be made to activate an oscillograph galvanometer (for photographic recording) or an ink writer. This N₂ meter has the fastest response time of any known analyzer; the over-all time for sampling, analyzing and recording 90 per cent of an abrupt change in gas composition is only 0.05 second. With the technic used in this test N₂ concentration can be read accurately within 0.5 per cent N₂. Use of this meter permits a detailed analysis of the changes in N₂ concentration that occur during the first expiration following a single inhalation of O₂.

The other instrument is a flow meter. We use a meter designed by Lilly¹⁰ which is similar in principle to that of Silverman.¹⁶ The subject expires through a double cone device which has a Monel metal or phospho-bronze screen (400 mesh) at the widest portion. This screen causes a slight resistance to gas flow and creates a difference in pressure on the two sides which can be measured by a differential electrical capacitance manometer. This pressure difference is proportional to the volume flow over the range of 0 to 260 L./min. It may be recorded photographically or by an ink writer. A typical record for expired gas is shown in Figure 1. The instantaneous volume flow (ml./sec.) may be measured as the vertical distance from the zero line to the curve at any point; volume of gas expired to any given point may be obtained by measuring the area between the curve and the zero line.

The actual technic is as follows: The subject's nose is closed with a clip and he breathes through a mouthpiece. A four-way stopcock is attached to the mouthpiece so that the subject can be made to inspire either air or O₂ through demand regulators and to expire through the flow meter. The sampling needle of the N₂ meter is inserted into the middle of the lumen of the mouthpiece just beyond the lips. The subject is asked to expire maximally, then inspire maximally and again expire maximally,

* The respiration of chronically anoxic patients is often reduced appreciably by the inhalation of oxygen; this introduces another variable in the test.

fairly evenly and rapidly.* During the first expiration the valve is turned so that the subject will breathe O_2 instead of air on the succeeding inspiration. The events recorded during the second maximal expiration (Fig. 1) provide all the data required for our test. When the subject

that expired early.* Fowler⁷ has reported his detailed analysis of this plateau. For clinical purposes we have arbitrarily decided to make only one measurement and that is to compare the N_2 concentrations at 750 and 1,250 ml. (BTPS) of expired gas to determine the magni-

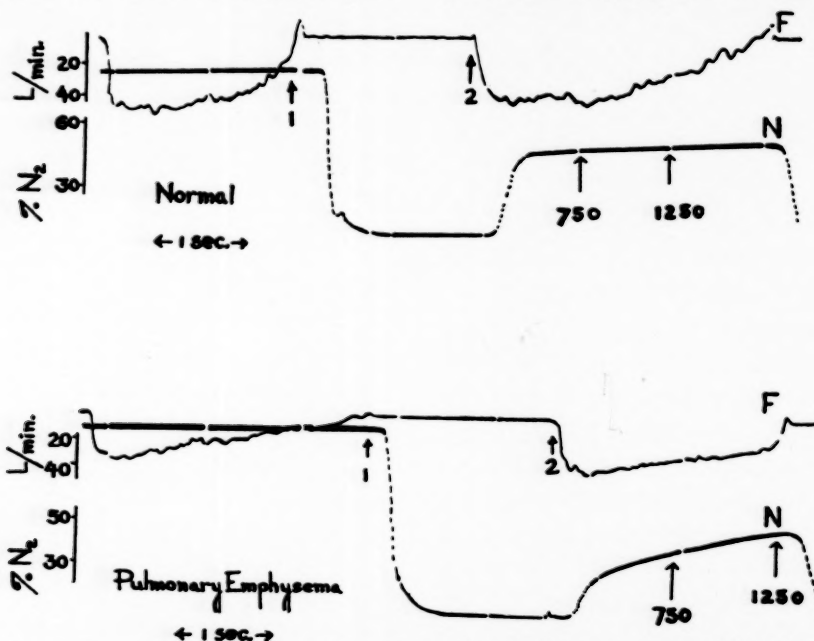


FIG. 1. Records of expiratory volume flow (F) and N_2 concentration (N) during voluntary hyperventilation. To left of 1, expiration after air breathing; from 1 to 2, inspiration of O_2 ; at 2 expiration begins. Between 750 and 1,250 ml., N_2 concentration increases 1 per cent in the normal record and 9 per cent in the record of the patient with emphysema.

inspires he draws in enough O_2 to lower the alveolar N_2 concentration appreciably. During expiration the first gas issuing through the mouthpiece is O_2 that remained in the respiratory dead space. The next phase (rapidly rising N_2 concentration) represents a mixture of dead space oxygen and that alveolar gas which washed it out. The last phase consists of alveolar gas, and it is this alveolar gas plateau that is important in our test.

If the inspired O_2 were distributed uniformly throughout all the alveoli, one would expect that this alveolar gas plateau would be a horizontal line. If gas distribution were non-uniform one might expect rising, falling or generally uneven plateaus; in our experience these almost invariably slope upward, i.e., the alveolar gas expired last has a higher N_2 concentration than

* It has been shown previously that the alveolar plateau is somewhat influenced by the volume of inspiration and the rapidity of expiration, becoming more horizontal as these are increased.⁷ However, it was found impractical to attempt to control these factors for clinical use.

tude of the slope. The 750 and 1,250 ml. points are measured on the flow record and the N_2 concentrations at the corresponding points on the N_2 record are then measured.† In healthy young adult subjects the N_2 concentration at 1,250 ml. is always the same or higher than that at 750 ml.; the mean increase at 1,250 ml. (compared with 750 ml.) in twenty-six tests upon fourteen subjects (age eighteen to thirty-eight, mean 28.2 years) was 0.7 per cent N_2 (S. D. \pm 0.3 per cent).

The first volume (750 ml.) is chosen because the subject is expiring pure alveolar gas at that point; it is safe to assume that the respiratory

* The nitrogen meter is not sensitive enough to detect variations in N_2 concentration that may result from 79.03 per cent N_2 (room air) is inspired and distributed unevenly in alveolar gas containing 80 per cent N_2 . However, when the inspired gas is 99.6 per cent O_2 , the effect of uneven mixing of 0.4 per cent N_2 with alveolar gas containing 80 per cent N_2 is readily apparent.

† In occasional subjects the plateau is wavy. In these cases a line is drawn to define by visual estimation the mean slope and N_2 concentrations are measured on this line.

dead space, even when enlarged by hyperventilation, is washed out completely by 750 ml. of expired gas. The second point (1,250 ml.) is chosen for two reasons: (1) Although it has been found that the increase in N_2 concentration per liter expired alveolar gas is fairly constant throughout most of the expired alveolar plateau, the N_2 slope may be irregular, rise rapidly or turn downward during the last several hundred milliliters of a maximal expiration in some patients. (2) Selection of points more widely separated than 750 and 1,250 ml. might reduce errors in measurement but many patients with pulmonary disease cannot expel larger volumes. Indeed, of 104 patients studied by our technic twenty were unable to expel 1,250 ml. after a maximal inspiration. However, in sixteen of these the N_2 concentration rose more than 2 per cent from the 750 ml. volume to the end expiratory volume and there was no difficulty in judging these to be abnormal. In two of the remaining four a volume of 500 ml. separating two points on the alveolar air plateau could be obtained by reading the first point at 650 ml. instead of 750 ml. This modification is justified if the transition from the rapidly rising N_2 curve (dead space washout) to the alveolar plateau has occurred prior to that volume and is readily identifiable.⁷ The other two cases were a child of nine years who could expel only 805 ml. and an adult with pulmonary carcinoma who could expel only 800 ml. Thus we were unable to measure the records from this test in only two of 104 instances.

Some patients experience difficulty in breathing as directed once a mouthpiece is inserted and must repeat the test. However, many more patients have difficulty delivering a true alveolar air sample in the seven-minute test.

RESULTS

A series of seventy-seven patients with pulmonary disease was studied by the seven-minute pulmonary emptying rate test of Cournand et al.⁴ The final N_2 concentration was obtained from the continuous N_2 meter record. Then after a suitable period for reestablishing N_2 equilibrium each patient was studied by the single breath test just described. An additional twenty-seven patients were studied by the latter test alone. It should be pointed out that there is no absolute standard against which

to compare either of these tests although considerable promise is shown by indices based on the recently reported multiphasic analysis of pulmonary N_2 elimination curves obtained during a several minute period of O_2 inhalation.^{8,13} All our patients had

TABLE I
PER CENT OF CASES JUDGED ABNORMAL BY PULMONARY
EMPTYING RATE TEST (P.E.R.) AND SINGLE BREATH
TEST (S.B.)

	All Cases			Patients Less Than Fifty Years Old		
	No. of Pa- tients	P.E.R. (Per cent)	S.B. (Per cent)	No. of Pa- tients	P.E.R. (Per cent)	S.B. (Per cent)
Asthma.....	22	41	82	17	24	76
Emphysema.....	12	75	100	1	100	100
Bronchiectasis.....	9	33	89	8	25	88
Sarcoid.....	9	0	67	7	0	57
Congestive heart failure.....	7	14	56	4	0	50
Pulmonary carcinoma.....	5	40	100	0
Post-pneumectomy.....	3	0	100	0
Miscellaneous.....	10	10	40	7	14	43
Totals.....	77	32	78	44	18	68

pulmonary disease or congestion of the pulmonary circulation, but we do not know whether all would have shown abnormalities in distribution if a theoretically perfect test had been applied.

The single breath analysis revealed abnormalities in 78 per cent of the whole group (Table I) while the Cournand test was positive in only 32 per cent. The single breath test showed abnormal gas distribution in all of the patients with emphysema; the Cournand test was abnormal in 75 per cent of these. Not only was the single breath analysis a more sensitive test of pulmonary emphysema but also it revealed abnormalities in the majority of patients with bronchiectasis, asthma, sarcoid, pulmonary carcinoma and congestive heart failure, whereas the seven-minute test did not. The false negative seven-minute tests were due in most cases to hyperventilation. It is true that some patients are unable to deliver properly the alveolar gas sample required in the seven-minute test; however, since we recorded continuously the volume flow and N_2 concentration we could and did eliminate these patients from the series.

COMMENTS

It is not generally recognized that uneven distribution can be a factor in a number of pulmonary diseases other than emphysema although there is ample reason to expect its occurrence.³ The manner in which inspired gas is distributed depends upon many factors which influence the timing and extent of alveolar ventilation. Some of the individual factors and instances in which they are changed by disease are (1) Decreased distensibility: certain areas of the lung may require a relatively greater force to expand them as the result of pulmonary fibrosis, congestion, carcinoma, sarcoid or pulmonary hemangioma. One would anticipate underventilation of such areas compared with normal areas. (2) Regional obstruction of air passages: such obstruction occurs in bronchial and bronchiolar lesions and opposes rapid ventilation of the obstructed parts. (3) Loss of elasticity: the normal elastic recoil of the lungs is an important factor in ventilation throughout each cycle; it opposes inflation during inspiration and becomes a major force deflating the lungs during expiration. Loss of elasticity in certain areas very probably alters the extent and timing of alveolar ventilation, relative to that of other areas. There may be, of course, combinations of changes in distensibility, elasticity and patency of airways in the same or different regions of the lungs.

The single breath test is a rapid, sensitive indicator of abnormal alveolar ventilation. In our experience it often reveals disturbances which are not demonstrated by the seven-minute test. However, we wish to emphasize several limitations of our test: (1) It demonstrates abnormalities only in the distribution of gas to alveoli and not in diffusion across the alveolo-capillary membrane, lung volume, pulmonary circulation or distribution of pulmonary blood flow to various alveoli. (2) A positive test indicates abnormal distribution but a normal curve does not necessarily rule out unusual or slight degrees of abnormal distribution.

The upward slope of the alveolar plateau depends both on uneven distribution of O₂ during inspiration and on the relatively late emptying of poorly ventilated areas. It is possible that synchronous emptying could produce a normal plateau despite abnormal

TABLE II
INCREASE IN N₂ CONCENTRATION (750–1,250 ML. EXPIRED GAS) DURING SINGLE BREATH TEST PERFORMED UPON SIXTY-ONE NORMAL INDIVIDUALS AND 104 PATIENTS WITH PULMONARY DISORDERS

	No. of Cases*	Mean Increase	Range
Normal, young . . .	26	0.7% ± 0.3	0.0–1.5
Normal, old†	25	1.8% ± 1.1	0.0–4.5
Asthma	24 (5)	3.8	0.5–8.5
Emphysema	17 (14)	6.9	3.0–12.0
Bronchiectasis	9 (1)	4.6	1.0–8.0
Sarcoid	9 (2)	3.4	1.0–6.0
Congestive heart failure	14 (5)	3.0	0.5–8.5
Pulmonary carcinoma	7 (7)	5.1	3.0–6.5
Post-pneumonectomy	5 (5)	4.2	2.0–7.5
Miscellaneous	19 (5)	2.7	0.5–8.5

* Numbers in parentheses refer to patients more than fifty years of age.

† Old normal data from Greifenstein et al.⁹

inspiratory distribution; this is unlikely although we suspect it occurred in one patient examined after pneumonectomy. (3) An abnormal single breath test is not diagnostic of any specific pulmonary disease. Although patients with pulmonary emphysema show the most decided and consistent deviations from normals, similarly marked abnormalities may occur in patients with bronchiectasis, asthma, congestive heart failure, carcinoma of the lung, silicosis or sarcoid. (Table II.) (4) Although the procedure seems ideally suited for mass testing, its usefulness for this purpose is at present limited to younger age groups because measurements on about half of elderly individuals (fifty to eighty-one years) with no clinical or radiologic evidence of pulmonary disease show "abnormalities"

relative to the findings in healthy subjects in the twenty to thirty-five year age group.⁹ Further studies are needed in children and in the thirty-five to fifty year range, and further studies are also necessary to establish the diagnostic and prognostic significance of changes found in certain elderly persons. (5) At present the apparatus is expensive and not commercially available.

This test obviously does not replace other tests of pulmonary function. However, it does provide the clinician with another diagnostic tool for the detection of many types of pulmonary disease. It is a non-specific test which calls attention to an abnormality the precise nature and significance of which must be determined by other technics. In our experience it is particularly valuable in those conditions in which roentgenographic technics reveal no abnormality or yield equivocal information and in obtaining objective evidence of certain aspects of pulmonary function in compensation cases.

SUMMARY

A new clinical test is described for the detection of certain types of pulmonary abnormalities. By continuous measurement of N₂ concentration and volume flow of alveolar gas expired after a single breath of O₂, it is possible to detect uneven distribution of inspired gas in the lungs. The test does not diagnose specific types of pulmonary disease but directs attention to a definite abnormality which can be explored more fully by other methods.

A comparison has been made in seventy-seven patients of this new test with the seven-minute pulmonary N₂ emptying rate of Cournand and associates. The single breath analysis revealed abnormal distribution in 77 per cent whereas the seven-minute test was abnormal in only 32 per cent.

The test is rapid, objective and requires

only a minimum of cooperation on the part of the patient.

REFERENCES

1. BATEMAN, J. B. Measurement of intrapulmonary mixing and pulmonary mid-capacity ("functional residual air"). *Proc. Staff Meet., Mayo Clin.*, 21: 112, 1946.
2. BIRATH, G. Lung volume and ventilation efficiency. *Acta med. Scandinav.*, Suppl., 154: 215, 1944.
3. COMROE, J. H., JR. The value of pulmonary function tests in the diagnosis of pulmonary disease. *Tr. & Stud., Coll. Physicians, Philadelphia*, 18: 49, 1950.
4. Cournand, A., Baldwin, E., Darling, R. C. and Richards, D. W. Studies on intrapulmonary mixture of gases. IV. Significance of pulmonary emptying rate and simplified open circuit measurement of residual air. *J. Clin. Investigation*, 20: 681, 1941.
5. DARLING, R. C., Cournand, A. and Richards, D. W. Studies on intrapulmonary mixture of gases. V. Forms of inadequate ventilation in normal and emphysematous lungs, analyzed by means of breathing pure oxygen. *J. Clin. Investigation*, 23: 55, 1944.
6. FOWLER, W. S. *Methods in Medical Research*, vol. 2, p. 226. Chicago, 1950. Yearbook Publishers.
7. FOWLER, W. S. Lung function studies. III. Uneven pulmonary ventilation in normal subjects and in patients with pulmonary disease. *J. Appl. Physiol.*, 2: 283, 1949.
8. FOWLER, W. S., CORNISH, E. R., JR. and KETY, S. S. Measurement of alveolar ventilatory components. *Am. J. M. Sc.*, 220: 112, 1950.
9. GREIFENSTEIN, F., KING, R. M., LATCH, S. S. and COMROE, J. H., JR. In press.
10. LILLY, J. C. *Methods in Medical Research*, vol. 2, p. 113. Chicago, 1950. Yearbook Publishers.
11. LILLY, J. C. *Medical Physics*, 2nd ed. Chicago, 1950. Yearbook Publishers.
12. LILLY, J. C. Mixing of gases within respiratory system with a new type nitrogen meter. *Am. J. Physiol.*, 161: 342, 1950.
13. ROBERTSON, J. S., SIRI, W. E. and JONES, H. B. Lung ventilation patterns determined by analysis of nitrogen elimination rates; use of the mass spectrometer as a continuous gas analyzer. *J. Clin. Investigation*, 29: 577, 1950.
14. ROELSEN, E. Fractional analysis of alveolar air after inspiration of hydrogen as a method for determination of distribution of inspired air in lungs. *Acta med. Scandinav.*, 95: 452, 1938.
15. ROELSEN, E. and BAY, N. Investigations of the lung function in silicotics. *Acta med. Scandinav.*, 103: 55, 1940.
16. SILVERMAN, L. Respiratory air flow characteristics and their relation to certain lung conditions occurring in industry. *J. Indust. Hyg. & Toxicol.*, 28: 183, 1946.

Effect of Nitroglycerine on the Cardiovascular System of Normal Persons*

RENÉ WÉGRIA, M.D., JOHN L. NICKERSON, PH.D., ROBERT B. CASE, M.D. and
JAMES F. HOLLAND, M.D.

New York, New York

LITTLE information is available about the effect of the nitrites on the output and work of the human heart; but because the nitrites are efficacious in stopping anginal pain due to temporary myocardial ischemia, it has been postulated that they do so by decreasing the work of the heart, or by increasing the coronary blood flow more than the work of the heart, or through both mechanisms. In 1915 Lindhard¹ showed that in normal persons the inhalation of amyl nitrite for two minutes produces a slight decrease in blood pressure and increases the cardiac output and heart rate. With more prolonged administration of the drug, however, the cardiac output is not modified and the blood pressure falls markedly. Gaisböck and Jarisch² studied the effect of subcutaneously injected sodium nitrite on the circulation of normal persons. They found that 0.01 and 0.02 gm. increase the cardiac output without affecting either blood pressure or heart rate. Other vasodilators such as histamine and carbaminoyl-chlorine have been shown respectively by von Euler and Liljestrand³ and by Wégria⁴ to have a similar action on the circulation. The purpose of this work was to study the effect of doses of nitroglycerine used clinically on the circulation of normal persons.

METHODS

Ten normal, healthy persons ranging in age from twenty-three to thirty-five were used as subjects. The cardiac output was determined with the ballistocardiograph.⁵

* From the Departments of Medicine and Physiology, College of Physicians and Surgeons, Columbia University, and the Presbyterian Hospital, New York, N. Y. This study was supported by a grant from the Life Insurance Medical Research Fund, Inc.

All subjects abstained from food and fluid for at least six hours except subjects H. H. and A. K. (Table 1) who took no food or fluid for three and a half hours. They all lay quietly on the ballistocardiograph bed for at least thirty minutes. Then blood pressure, heart rate and cardiac output were determined at intervals of a few minutes. After several control values were obtained, five subjects were given a placebo (one or two tablets of lactose) and the effects of the placebo were observed for ten to fifteen minutes. Five subjects were not given any placebo. Each of the subjects was given 0.0006 gm. nitroglycerine in one or two tablets and was told to allow the tablets to dissolve under the tongue and to swallow the saliva when necessary. In one experiment the determination of the cardiac output after nitroglycerine simultaneously with the ballistocardiograph and by cardiac catheterization yielded qualitatively similar results.†

RESULTS AND COMMENTS

The results are summarized in Table 1. In one of the five subjects to whom a placebo was given (subject R. C.) there was a temporary increase in the cardiac output after the administration of the placebo. In all ten subjects 0.0006 gm. nitroglycerine increased the cardiac output by a minimum of 25 per cent (subject J. R.) to a maximum

† The authors are indebted to Drs. E. deF. Baldwin and D. E. Green for determining the cardiac output by direct cardiac catheterization in this study.

TABLE I

Cardiac Output (L./min.)	Systolic Output (cc.)	Blood Pressure (mm. Hg)		Heart Rate (beats per min.)	Time (min.)*
		Systolic	Diastolic		
H. P.					
4.6	77	120	75	60	0
4.6	85	114	80	54	3
4.6	88	120	80	52	6
4.1	82	118	70	50	10
4.6	92	116	70	50	12
4.2 [†]	88	116	70	48	15
4.0	83	114	70	48	17
4.2	84	116	75	50	19
5.0	100	120	80	50	22
4.4	82	114	76	54	25
4.7	94	116	75	50	28
4.8	96	118	75	50	30
5.0	100	118	85	50	31
7.4	119	118	90	62	35
7.1	111	110	90	64	37
7.9	119	120	90	66	40
7.5	114	116	85	66	44
6.0	100	116	82	60	46
6.2	107	116	80	58	51
6.6	114	120	85	58	56
7.0	130	120	85	54	60
6.1	113	118	90	54	64
7.2	129	116	85	56	67

Cardiac Output (L./min.)	Systolic Output (cc.)	Blood Pressure (mm. Hg)		Heart Rate (beats per min.)	Time (min.)*
		Systolic	Diastolic		
H. H.					
5.9	87	110	70	68	0
5.8	88	110	70	66	3
5.7	81	110	70	70	5
6.0	88	110	70	68	8
5.7	84	110	70	68	11
5.5	81	110	65	68	12
6.2	97	110	70	64	13
5.8	85	110	70	68	16
6.0	88	112	70	68	18
6.4	89	110	70	72	21
5.7	79	108	70	72	22
5.6	80	110	70	70	23
7.0	100	116	72	70	25
7.5	91	118	80	82	27
8.6	105	114	80	82	30
7.0	88	110	78	80	33
7.3	96	110	72	76	35
6.5	90	108	70	72	39
6.8	94	110	74	72	43
6.6	87	118	70	76	46
7.4	95	116	75	78	49

J. R.					
3.6	78	110	60	46	0
3.6	82	110	60	44	3
3.5	76	112	65	46	7
3.5	76	110	65	46	9
3.4	74	115	65	46	12
3.4	74	110	60	46	13
3.7	77	116	65	48	16
3.4	74	116	65	46	18
3.4	74	114	65	46	20
3.6	78	116	65	46	22
4.0	77	112	70	52	24
4.4	92	110	70	48	27
4.5	87	108	70	52	28
4.4	85	108	70	52	30
4.4	85	110	60	52	32
4.1	82	105	60	50	35
4.1	79	108	60	52	38
3.8	76	108	70	50	40
3.7	80	108	70	46	42
3.5	76	108	70	46	44

R. C.					
5.6	82	120	75	68	0
5.7	81	115	80	70	2
5.9	84	120	80	70	3
5.8	85	120	80	68	4
5.6	85	115	75	66	6
6.8	89	125	85	76	8
7.2	95	130	80	76	10
5.8	76	130	90	76	13
5.7	77	120	80	74	15
5.3	74	125	85	72	17
5.5	79	125	80	70	20
8.0	77	130	90	104	23
13.2	138	130	90	96	25
9.1	97	125	90	94	26
10.1	115	110	85	88	28
9.8	117	115	85	84	29
10.0	119	120	80	84	31
11.2	127	115	80	88	33
10.0	116	115	80	86	35
10.3	129	110	80	80	38
7.6	103	115	80	74	41
6.4	86	110	80	74	44

* Minutes from time of first determinations.

† In each study the placebo was given at the time indicated by the single horizontal line and the nitroglycerine was given at the time indicated by the double horizontal line.

TABLE I (Continued)

Cardiac Output (L./min.)	Systolic Output (cc.)	Blood Pressure (mm. Hg)		Heart Rate (beats per min.)	Time (min.)*	Cardiac Output (L./min.)	Systolic Output (cc.)	Blood Pressure (mm. Hg)		Heart Rate (beats per min.)	Time (min.)*
		Systolic	Diastolic					Systolic	Diastolic		
A. K.						R. D.					
3.4	59	100	62	58	0	4.4	73	100	70	60	0
3.5	63	104	64	56	3	4.6	79	105	70	58	2
3.0	54	98	66	56	6	4.6	77	105	70	60	3
3.4	61	100	62	56	8	5.7	92	110	70	62	6
3.5	63	102	60	56	12	6.7	108	100	70	62	7
4.0	74	102	62	54	15	7.8	115	105	70	68	9
3.4	59	104	70	58	17	8.2	117	105	75	70	11
4.4	76	104	70	58	20	7.7	116	105	75	66	13
3.1	62	100	65	50	26	8.3	118	105	75	70	15
7.0	109	108	75	64	28	7.5	110	105	75	68	16
6.0	77	100	70	78	31	7.5	107	105	75	70	18
5.5	72	102	75	76	32	7.7	107	105	70	72	21
4.9	79	100	70	62	36	8.5	129	105	75	66	25
4.7	76	100	70	62	38	9.0	140	100	75	64	27
5.1	85	100	70	60	40	7.4	123	105	70	60	31
4.6	82	100	70	56	44	7.5	121	105	75	62	32
4.5	80	98	70	56	48	8.2	136	105	75	60	34
4.0	77	95	68	52	50	J. M.					
4.1	79	100	70	52	54	6.4	97	110	70	66	0
J. H.						6.9	96	110	70	72	2
5.0	83	100	60	60	0	7.3	107	115	70	68	4
5.5	92	105	65	60	3	5.9	98	110	70	60	6
4.8	80	110	65	60	6	7.0	103	110	70	68	8
5.0	83	100	65	60	8	7.9	110	110	70	72	9
6.3	98	110	70	64	11	9.9	112	110	75	88	11
7.0	100	110	70	70	13	10.3	120	110	80	86	13
7.7	107	110	70	72	16	8.7	103	110	80	84	14
7.6	91	100	70	84	19	10.5	117	105	75	90	16
9.3	126	105	75	74	24	8.9	103	110	75	86	18
7.4	103	100	70	72	29	7.5	91	105	75	82	20
7.6	112	105	70	68	33	7.7	96	105	75	80	21
A. M.						7.6	97	110	75	78	23
4.2	75	105	70	56	0	9.0	112	110	80	80	25
4.8	83	100	70	58	2	7.5	101	110	75	74	28
4.9	85	100	70	58	3	7.0	100	110	75	70	31
4.6	77	100	70	60	4	6.9	96	110	75	72	34
4.8	89	100	65	54	6	R. W.					
4.8	92	100	70	52	8	5.8	104	100	70	56	0
4.6	79	100	70	58	10	6.1	109	100	70	56	3
6.1	91	100	70	67	12	6.1	109	100	70	56	5
7.5	101	100	70	74	15	6.4	114	100	70	56	8
6.8	90	95	75	76	16	6.3	112	100	70	56	10
6.8	100	95	75	68	18	7.1	115	95	70	62	13
7.5	114	100	70	66	22	8.5	125	90	70	68	17
7.7	113	95	75	68	24	8.6	130	95	70	66	19
8.2	114	95	70	72	26	8.0	138	100	65	58	20
7.1	99	95	65	72	29	7.0	113	100	75	62	25
7.3	107	100	70	68	31	7.2	124	95	65	58	27
						6.8	121	100	70	56	29

of 124 per cent (subject R. C.) of the highest control value. The increase in cardiac output was definite from one to seven minutes and the maximal increase occurred from two to twenty-four minutes after the tablet of nitroglycerine had been placed in the mouth. The cardiac output resumed its control value within twenty to twenty-four minutes in three cases (subjects J. R., A. K. and J. M.). In the other seven cases it was still increased at the time the observations were discontinued, from nineteen to thirty-seven minutes after the administration of nitroglycerine.

The increase in cardiac output was due partly to an increase in heart rate and partly to an increase in systolic output although when the increase in cardiac output was waning it was occasionally due exclusively to an increase in systolic output. The changes in blood pressure were not marked and most of the time the systolic and diastolic blood pressures did not change, or rose slightly. Since the cardiac output per minute and the systolic output were both increased whereas the blood pressure was not significantly altered by nitroglycerine, it must be concluded that the work of the heart per minute and per beat was increased by the dose of nitroglycerine administered.

The mechanism of the increase in cardiac output is of interest. *A priori*, it is possible that the primary action of nitroglycerine is to increase the venous return to the heart by opening wider communications between arteries and veins. The increased cardiac output would then be the result of vasodilatation. Another possibility is that the vasodilator effect of nitroglycerine leads to an ephemeral decrease in blood pressure which acts by way of carotid sinus and aortic arch reflexes to increase reflexly heart rate and cardiac output.⁶ Obviously the two mechanisms are not mutually exclusive. Whether other mechanisms such as the Bainbridge reflex play a role in the phenomena observed cannot be determined from our experiments. Whatever the intimate mechanisms of the increase in cardiac

output produced by nitroglycerine may be, the work of the heart per minute and per beat is increased since both cardiac output per minute and systolic output are increased whereas the blood pressure is not altered by the dose of nitroglycerine administered. If our observations, made on normal subjects lying horizontally under almost basal conditions, apply to patients having an attack of angina pectoris, it must be concluded that nitroglycerine relieves cardiac pain by increasing the coronary flow more than the work of the heart and not by decreasing the work of the heart. Our observations are also of practical interest. One may wonder what happens when nitroglycerine is given to a patient who has anginal pain not because of myocardial ischemia but because of coronary occlusion. Nitroglycerine, indeed, is given to patients who have anginal pain because of myocardial ischemia; but when such patients have an attack of angina because they finally have had a coronary occlusion, they often take several nitroglycerin tablets in succession as their pain is not relieved. One can easily visualize that such a practice may lead, through the mechanism previously discussed, to an undesirable increase in the work of an already handicapped myocardium or to shock if the myocardial reserve has been too drastically jeopardized by the infarction.

CONCLUSIONS

The effect on the cardiovascular system of doses of nitroglycerine used clinically (0.0006 gm.) was studied in ten normal persons.

Cardiac output per minute, systolic output and heart rate were observed to increase whereas the blood pressure did not change. The cardiac work per beat and per minute is therefore increased by the dose of nitroglycerine employed.

These findings suggest that nitroglycerine relieves the anginal pain of myocardial ischemia by increasing the coronary flow relatively more than the work of the heart. They would also appear to suggest a

physiologic basis for caution in using nitroglycerine when the cause of the anginal pain is not definitely established to be simple temporary myocardial ischemia and may be due to coronary occlusion.

REFERENCES

1. LINDHARD, J. Ueber das Minutenvolumen des Herzens bei Ruhe und bei Muskelarbeit. *Arch. f. d. ges. Physiol.*, 161: 233, 1915.
2. GAISBÖCK, F. and JARISCH, A. Ueber den Einfluss von Natrium nitrosum auf den Kreislauf. *Wien. klin. Wchnschr.*, 40: 1540, 1927.
3. VON EULER, U. and LILJESTRAND, G. Die Wirkung von Adrenalin, Sympathol, Thyramin, Ephetonin und Histamin auf Gaswechsel und Kreislauf beim Menschen. *Skandinav. Arch. f. Physiol.*, 55: 1, 1929.
4. WÉGRIA, R. Action de quelques médicaments sur le débit cardiaque. *Arch. internat. de pharmacodyn. et de therap.*, 55: 156, 1937.
5. NICKERSON, J. L., WARREN, J. V. and BRANNON, E. S. The cardiac output in man; studies with the low frequency critically-damped ballistocardiograph and the method of right atrial catheterization. *J. Clin. Investigation*, 26: 1, 1947.
6. CHARLIER, R. Le rôle des régions sinuaires et cardio-aortique dans la régulation réflexe du débit cardiaque. *Acta cardiol.*, 1: 1, 1948.

The Natural Course of Rheumatoid Arthritis and the Changes Induced by ACTH*

JOSEPH E. GIANIRACUSA, M.D., MARIAN W. ROPES, M.D., J. PETER KULKA, M.D. and
WALTER BAUER, M.D.

Boston, Massachusetts

THE course of rheumatoid arthritis is characterized by spontaneous remissions which are unpredictable in time and duration. The variability of the natural course of this disease can be appreciated only after long-continued study of a large, unselected group of patients. Observations of this type on a large series of rheumatoid arthritis patients during the past twenty-two years have made possible a better definition of the natural course of the disease and have provided a control series by which the effects of therapeutic measures may be evaluated.¹ In addition, we have learned that rheumatoid arthritis is a generalized disease characterized by well marked constitutional manifestations which may be the first symptoms experienced by the patient and are not merely secondary to the articular lesions.²

The value of such long-continued observations is well exemplified by the case of a young woman with rheumatoid arthritis who between 1942 and 1949 was studied carefully during the initial period of active disease and during spontaneous remission and postoperative exacerbation. This background provided a unique opportunity to observe the effect of ACTH on the clinical and laboratory manifestations of rheumatoid arthritis³ and to compare the hormone-induced changes with those which occur spontaneously. This phase of the study extends over a ten-month period and includes observations on an ACTH-in-

duced remission and two ACTH withdrawal exacerbations. The effect of ACTH on articular inflammation, as determined by microscopic examination of synovialis before and after the ACTH-induced remission, was studied; synovial membrane biopsied during the spontaneous remission was available for comparison.

The purpose of this paper is to report these observations, particularly as they concern similarities and differences between the spontaneous and ACTH-induced remissions and the postoperative and ACTH withdrawal exacerbations, and to discuss the implications of this long-term study.

When the patient first came under our observation (1942), she was fourteen years old and had been ill for about eighteen months. The initial symptoms consisted of pain in the feet, followed in a few months with pain, swelling and tenderness in the knee, elbow and wrist joints and in the small joints of the hands. The illness was accompanied with low grade fever, vasomotor symptoms, anorexia and moderate loss of weight. The articular involvement was progressive and soon led to limitation of motion in the wrist and elbow joints. The physical findings were typical of rheumatoid arthritis with pain, swelling, tenderness and limitation of motion of the involved joints. The laboratory studies and x-ray examinations corroborated the diagnosis.

Physical examination: Temperature, 98.6°F. Appearance: thin and pale. Skin: no rash or subcutaneous nodules. Hyperhidrosis of palms and soles. Lymph nodes: minor cervical and

* From the Medical Clinic, Massachusetts General Hospital, the Department of Medicine, Harvard Medical School, and the Massachusetts Department of Public Health, Boston, Mass. This is publication No. 119 of the Robert W. Lovett Memorial for the study of crippling disease, Harvard Medical School. The expenses of this investigation were defrayed in part by a grant from the Commonwealth Fund.

inguinal lymphadenopathy. Lungs: normal. Heart: normal. Abdomen: no organs or masses palpable. Joints: Cervical spine: stiff but not limited in motion. Shoulders: normal. Elbows: swollen and tender with 15 degrees of permanent flexion and 75 degrees of further flexion on the right; 10 degrees of permanent flexion and normal further flexion on the left. Slight limitation of pronation and supination, more so on the right. Wrists: swollen and tender, left more so than right. Motion normal in the right wrist but extension limited to 40 degrees in the left. Second right proximal interphalangeal joint: swollen, tender and held in flexion. Hips: normal. Knees: swollen, tender with normal motion. Effusion present in each knee joint. Ankles: swollen and tender. Metatarsophalangeal joints: Swollen and tender, especially second and third.

Laboratory work: sedimentation rate, hematocrit and hemoglobin. (Fig. 1.) Non-protein nitrogen 18 mg. per 100 cc. Uric acid 1.4 mg. per 100 cc. Fasting glucose 64 mg. per 100 cc.

X-ray examinations: Knees: effusion in the left; joint surfaces and bones normal. Wrists and hands: some atrophy of bones; slight soft tissue swelling about several proximal interphalangeal joints and about right wrist; minimal irregularity of joint surfaces of ulnas. Elbows: narrowing of joint spaces bilaterally with some atrophy of bones. Feet: areas of decalcification of head of left fifth metatarsal.

The distribution of the serum proteins as determined electrophoretically will be found in Figure 1 and Table IA.

Synovial fluid: Left knee (twenty-third hospital day): color yellow, clot none, red blood cells 200, white blood cells 10,850, with 64 per cent polymorphonuclears, 22 per cent monocytes, 14 per cent lymphocytes, mucin poor, mucin nitrogen 0.28 gm. per 100 cc., mucin glucosamine .022 gm. per 100 cc., protein 5.4 gm. per 100 cc. Left knee (ninety-fourth hospital day): color reddish yellow, clot 2+, viscosity 5.4, red blood cells 18,300, white blood cells 17,200 with 79 per cent polymorphonuclears, 7 per cent monocytes, 14 per cent lymphocytes. Right knee (ninety-fourth hospital day): color reddish yellow, cloudy, clot 2+, viscosity 5.6, mucin poor, mucin nitrogen 0.10 gm. per 100 cc., mucin glucosamine 0.18 gm. per 100 cc., protein 5.2 gm. per 100 cc. Right knee (168th hospital day): color red, red blood cells 490,000, white blood cells 25,900, with 79 per cent poly-

morphonuclears, 9 per cent monocytes, 12 per cent lymphocytes. The electrophoretic distribution of proteins in these fluids resembled closely that in the sera obtained at the same time, except for a tendency toward an increasing concentration of gamma globulin in the fluid. (Table IB.)

The alterations in serum protein fractions were similar to those observed previously in

TABLE IA
ELECTROPHORETIC DISTRIBUTION OF PROTEINS IN 1.87 PER CENT SOLUTIONS OF SERUM IN SODIUM DIETHYLBARBITURATE BUFFER OF PH 8.55 AND IONIC STRENGTH 0.1

Date	Serum					
	Albu- min	Globulins				
		α_1	α_2	β	ϕ	γ
Per cent						
12/17/42	45.2	7.6	18.2	13.0	16.9
2/16/43	45.4	7.6	12.9	15.7	18.4
5/11/43	47.0	7.3	12.8	13.7	19.1
5/11/44	53.4	6.0	12.0	14.0	14.6
10/19/44	60.3	4.9	10.3	14.3	10.2
2/15/45	62.5	4.6	9.5	13.7	9.7
6/13/46	49.9	7.3	13.7	14.5	14.6
7/25/46	51.1	7.0	12.5	15.4	14.0
9/10/46	48.4	7.2	13.6	14.3	16.5
9/24/46*	44.7	7.4	12.6	12.3	10.2	12.8
10/22/46*	40.6	9.1	13.7	13.8	10.0	12.9
11/19/46*	41.5	7.8	13.3	13.2	9.2	14.0
12/24/46*	44.5	6.9	11.9	13.7	9.1	13.9
1/21/47*	46.7	7.0	12.3	12.4	7.6	14.0
6/26/47*	45.6	6.5	12.5	12.2	9.3	13.7
1/15/48*	48.0	6.3	10.8	14.5	8.6	11.9
10/28/48*	46.9	6.5	12.1	13.4	8.1	13.0
2/17/49*	44.3	7.1	12.4	13.0	9.3	13.9
7/20/49	47.8	6.5	12.2	15.9	17.6
8/18/49	49.4	5.9	11.8	15.0	17.9
9/1/49	55.9	5.1	11.2	13.3	14.5
9/15/49	55.4	5.5	11.1	16.2	11.8
10/21/49	58.2	5.5	10.7	16.1	9.5
11/3/49	53.0	7.4	13.2	16.1	10.3
12/9/49	56.3	6.2	13.9	13.7	9.9
12/24/49	57.0	6.7	12.7	16.6	7.0
1/4/50	49.5	8.3	15.8	18.5	7.9
1/9/50	44.5	9.2	15.6	19.0	11.7
1/20/50	47.6	6.5	12.5	17.5	15.9
1/30/50	51.4	6.1	11.1	16.0	15.4
3/2/50	56.7	5.4	10.1	14.3	13.4
5/8/50	57.6	5.2	11.0	13.6	12.6

* Patterns of plasma rather than serum.

cases of active rheumatoid arthritis,⁴ namely, an increase in alpha-1, alpha-2 and gamma globulin and fibrinogen fractions and a marked reduction in albumin fraction. (Fig. 1.) Results obtained in other cases suggest elevation of alpha globulins during

TABLE IB
ELECTROPHORETIC DISTRIBUTION OF PROTEINS IN 1.87 PER CENT SOLUTIONS OF SYNOVIAL FLUID IN SODIUM DIETHYL-BARBITURATE BUFFER OF PH 8.55 AND IONIC STRENGTH 0.1

Date	Joint Fluid				
	Albu- min	Globulins			
		α_1	α_2	β	γ
	Per cent				
12/17/42	47.6	8.5	12.9	14.2	16.8
2/16/43	50.7	7.8	10.6	12.0	18.9
5/11/43	47.6	6.9	12.5	9.5	23.5
7/20/49	48.4	7.6	9.7	11.0	23.3
8/18/49	49.9	5.6	8.2	12.0	24.4

the early course of the disease, followed later with a predominance in gamma globulin. As discussed later, this was the evolution in the present case.

Evaluation of the synovial fluid findings depends upon definition of the characteristics of normal synovial fluid⁵ and the alterations produced by disease in synovial tissues.⁶ Normal synovial fluid is a dialysate of plasma containing albumin, globulin and mucin. It is relatively cell poor, the average nucleated cell count being 63 per cu. mm. The average differential cell count is 63 per cent mononuclear phagocytes, 24.6 per cent lymphocytes, 6.5 per cent polymorphonuclear leukocytes, 4.3 per cent synovial cells and 2.2 per cent unidentified cells.

The average relative viscosity is 188 at 38°C. The study of normal cattle synovial fluid by electrophoresis reveals the presence of albumin, alpha-1, alpha-2, beta and gamma globulins and a component that moves faster than albumin. This fast-moving component, hyaluronic acid, is a polysaccharide containing equal amounts of acetyl-glucosamine and a uronic acid.

Addition of acetic acid to normal fluid to a final concentration of 1 per cent causes precipitation of mucin as a tough, ropey clump with clear surrounding solution. The average content of mucin nitrogen is 0.07 gm. N per 100 cc. Alterations in synovial fluid vary with the type, duration and severity of tissue inflammation.⁶ In mild cases of rheumatoid arthritis the changes in the fluid are slight. With increasing severity of disease the alterations usually increase, although the degree of change is not directly proportional to the severity. The correlation between cell count and severity is usually not close. However, a low fluid glucose level, a low viscosity and a poor mucin precipitate, and an electrophoretic distribution of fluid proteins similar to that in serum (abnormalities noted in our patient) suggest severe rheumatoid arthritis.

The patient was treated in the hospital for a period of six months. The therapeutic program used in this clinic consists of absolute bed rest, high caloric diet, aspirin for analgesia, moist heat to affected joints, bed exercises intended to maintain and gain articular function and discussion concerning emotional factors. The manifestations of active disease continued unabated for four or five months. (Fig. 1.) During the latter part of the hospital stay a favorable trend was suggested by decrease in malaise, anorexia and articular pain and by gain in weight. However, progressive flexion deformities of the elbows developed and signs of active synovitis persisted. Moreover, the usual laboratory studies suggested continued activity of the disease process. The sedimentation rate was as rapid during the last two months of hospitalization as during the first two months. (Fig. 1.) The hematocrit was 40 per cent or higher during the last three months, but this change came only after transfusion of 1,000 cc. of whole blood. (Fig. 1.) The synovial fluid studies were not complete enough to suggest a trend either toward or away from normal. On the other hand, the serum protein fractions after a four and one-half month

interval showed a significant increase in the albumin fraction. The change in alpha-2 and gamma globulin fractions was not in the same direction, alpha-2 globulin falling and gamma globulin rising. This is probably a function of the stage of disease, as the

after discharge objective signs were present only in the left knee, which was the site of marked soft tissue swelling, and the elbows, which showed a progressive loss of motion. During the next three months, however, no further improvement occurred. Because of

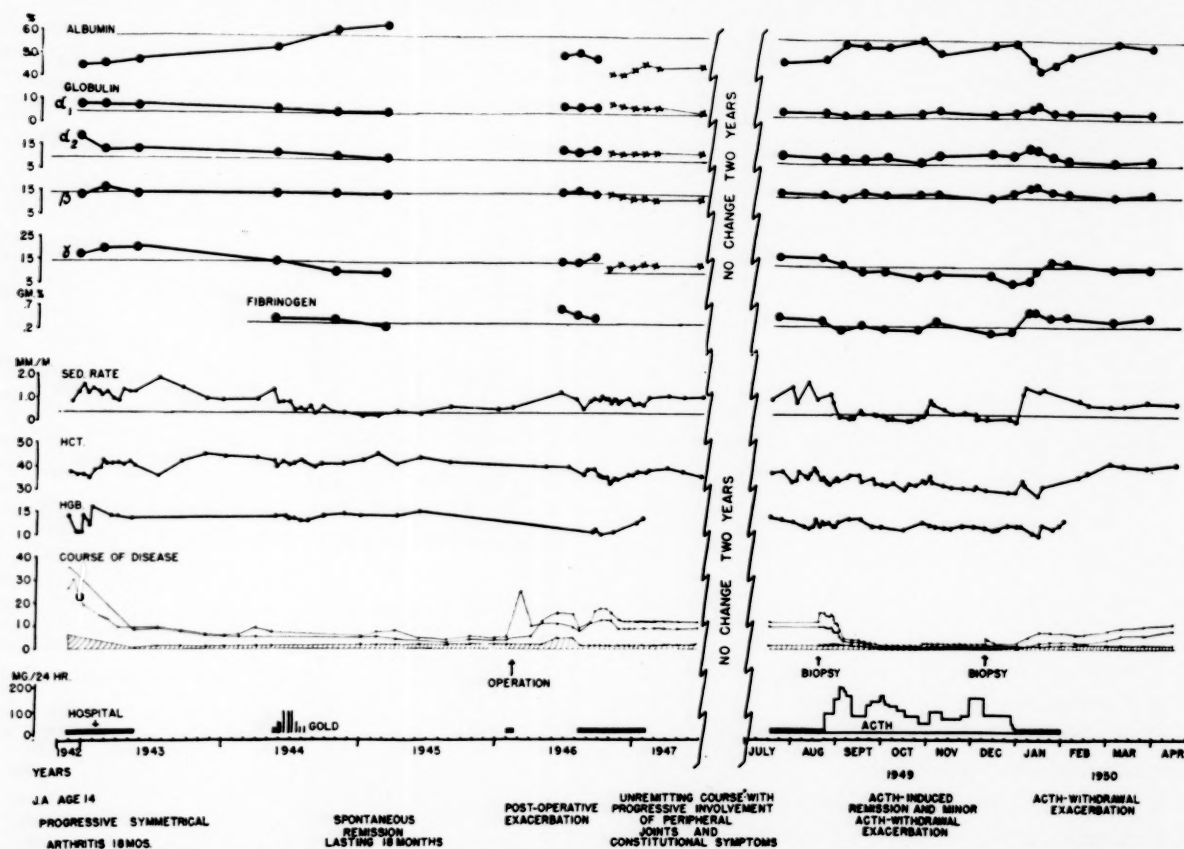


FIG. 1. Graphic representation of clinical course, hemoglobin, hematocrit, sedimentation rate and distribution of proteins determined electrophoretically during the total period of observation. The crosses (x) in electrophoretic patterns represent instances in which analyses were done on plasma rather than serum.

rise of alpha globulins occurs early and the characteristic rise of gamma globulin is a relatively late change. It has been our experience that the protein pattern changes in the direction of normal or may return to normal as the disease becomes quiescent.⁷

The patient was discharged with the disease still in the active phase. The therapeutic program was continued although lacking the close supervision possible in a hospital. During the first nine months of follow-up study there was slow but significant improvement. (Fig. 1.) This was manifested by further decrease in constitutional and articular symptoms. Ten months

the stationary state the patient seemed to be a suitable subject for evaluation of gold therapy. (Fig. 1.) The administration of gold sodium thiomalate (myochrysine (E), total dosage 600 mg.) was terminated after a period of four months owing to the appearance of a persistent leukopenia. Although the sedimentation rate decreased somewhat during this time, clinical improvement, coincident with a further fall to normal of the sedimentation rate, did not begin until one month after the cessation of chrysotherapy. It is our belief that gold therapy exerted no significant effect on the course of this patient's disease. The reasons for this

belief depend in part upon our total experience with chrysotherapy and so a brief digression on the general subject seems in order.

The experience at the Massachusetts General Hospital with gold therapy was reported in 1946.⁸ Some improvement was observed in nearly the same proportion of patients treated with gold as in the controls. The results of serial sedimentation rate determinations roughly paralleled the degree of clinical improvement. Further experience at this Clinic merely supports the conclusion expressed in 1946, "The burden of proof is still on the proponents of gold therapy to demonstrate by adequately controlled studies with a follow-up of three to five years that a significant effect is exerted on the course of rheumatoid arthritis by the administration of gold salts." It might be argued that the eighteen-month post-gold follow-up on this patient demonstrates an additive therapeutic effect on the part of gold. This possibility cannot be denied categorically. However, review of the data in Figure 1 is not in keeping with this interpretation. One notes that the gradient of clinical improvement was steep and had leveled off just three months prior to chrysotherapy. The sedimentation rate was decreasing gradually and reached near normal values during the first few weeks of gold therapy. Most important, the serum protein fractions had shifted significantly in the direction of normal before the first injection of gold. The temporal relationships point to a spontaneous remission unrelated to the administration of gold.

During the eighteen months following gold therapy constitutional and articular symptoms were minimal. Toward the end of that period limited physical activity was well tolerated as regards clinical signs and symptoms, in spite of a gradual increase in the sedimentation rate. The disease appeared to be almost quiescent, the principal problem being painless flexion deformities of both elbows. Readmission to the Massachusetts General Hospital was advised for surgical treatment of these joints.

Physical examination: Appearance: a fairly well developed and well nourished girl. Skin: no subcutaneous nodules. Marked hyperhidrosis of palms and soles. Lymph nodes: minor cervical and inguinal lymphadenopathy. Lungs: normal. Heart: normal. Abdomen: no organs or masses palpable. Joints: Elbows permanent flexion of 45 degrees with further flexion to 75 degrees. Knees: normal motion with only slight thickening of soft tissue structures.

Laboratory examinations: sedimentation rate 0.55 mm. per minute. Hematocrit 40 per cent. (Fig. 1.)

X-ray examinations: slight soft tissue swelling about both elbows; progression of the sclerosis of the trochlear notch of both ulnas with secondary degenerative changes anteriorly and posteriorly. The bones of both elbows appear more osteoporotic; the joint spaces are slightly narrowed, the left more so than the right.

The operation performed was excision of the head of the left radius. Microscopic study of the synovial membrane showed an active synovitis. (Fig. 9.) Although little motion was gained, the postoperative course was uneventful. She was discharged thirteen days after the operation.

Soon after discharge the patient noted increasing fatigue and concomitantly pain and swelling in knees, ankles, shoulders and fingers. She was re-admitted four months later with the hope that a conservative program would lead to an early remission. The principal objective change was swelling of both knees and the appearance of a subcutaneous nodule.

Physical examination: Appearance as before. Skin: small subcutaneous nodule over the right olecranon. Marked hyperhidrosis of palms and soles. Lymph nodes: minor cervical and inguinal lymphadenopathy. Lungs: normal. Heart: normal. Abdomen: no organs or masses palpable. Joints: Spine: normal. Shoulders: normal. Elbows: permanent flexion of 70 degrees and further flexion to 135 degrees on the right and permanent flexion of 45 degrees and further flexion to 135 degrees on the left. Wrists: extension 45 degrees, flexion 70 degrees. Fingers: stiff but not swollen. Hips: normal. Knees: soft tissue swelling and thickening; no fluid and normal motion. Metatarsophalangeal joints: tender.

Laboratory examinations: sedimentation rate, hematocrit, hemoglobin and electrophoretic pattern of serum proteins. (Fig. 1.) Non-protein

nitrogen 20 mg. per 100 cc.; prothrombin time twenty-five (19) seconds.

X-ray examinations: Hip joints and sacroiliac joints: normal.

Again there was a marked change in the protein pattern as determined electrophoretically. (Fig. 1.) One notes a marked reduction in albumin fraction and increase in alpha-1 and alpha-2 and gamma globulin and fibrinogen fractions during this exacerbation. The sedimentation rate paralleled these abnormalities.

For the first two months activity of the disease process was constant. (Fig. 1.) Although the articular involvement was persistent and progressive, during the latter half of the six months' hospital period, the symptoms abated somewhat. The suggestive symptomatic improvement paralleled a slight but definite trend toward normal in the sedimentation rate and serum protein fractions.

Joint examination at the time of discharge: Spine: normal. Shoulders: slight limitation of rotation. Elbows: permanent flexion of 60 degrees with further flexion to 135 degrees on right; permanent flexion of 45 degrees with further flexion to 135 degrees on the left. Wrists: extension 45 degrees and flexion 80 degrees on right; extension 45 degrees, flexion 60 degrees and radial deviation on left. Proximal interphalangeal joints: fusiform swelling and 10 degrees permanent flexion. Hips: normal. Knees: moderate thickening of periarticular tissues, right and left, with permanent flexion of 5 degrees and further flexion to 170 degrees on left. Metatarsophalangeal joints: slight tenderness and limitation of motion.

During the next twenty-seven months of Clinic follow-up the disease process was persistently active, as judged by clinical and laboratory criteria. (Fig. 1.) Ease of fatigue and pain and stiffness in the knees were the predominant symptoms. In addition, there was gradual loss of function and progressive deformity of many of the involved joints. The long-continued and detailed study of this patient and the unremitting nature of the disease following the exacerbation provided an excellent opportunity to study the effects of ACTH. Accordingly, in July, 1949, she was readmitted to the hospital for this purpose.

Physical examination revealed the extra-articular findings previously described. No nodules. Joints: Spine: normal. Shoulders: slight limitation of rotation. Elbows: permanent flexion of 80 degrees and further flexion to 130 degrees on the right; permanent flexion of 80 degrees and further flexion to 115 degrees on the left. Supination moderately restricted on the left side. Wrists: extension 45 degrees, flexion 50 degrees on the right; extension 5 degrees, flexion 60 degrees, moderate radial deviation on the left. Metacarpophalangeal joints: lacked 10 to 20 degrees of full extension and flexion; swelling and tenderness. Proximal interphalangeal joints: permanent flexion of 30 degrees to 80 degrees. Terminal interphalangeal joints: hyperextension of 20 to 30 degrees. Fist incomplete and grip poor. Hips: normal. Straight leg raising: poor. Knees: moderate tenderness and thickening of periarticular tissues, moderate effusions, full extension but flexion 150 degrees on right and 120 degrees on left. Ankles: flexion to 30 degrees. Metatarsophalangeal joints: slight limitation of motion and slight tenderness. She was unable to rise unaided from a sitting position and could walk only short distances with the help of crutches.

Laboratory examinations: see Figure 2 and tables in text.

X-ray examinations: lumbar and sacral spines are normal except for osteoporosis. The symphysis pubis is irregular and narrowed. Changes in joints of the hands, wrists, elbows, shoulders, knees and feet have progressed. The joints exhibit generalized osteoporosis, pronounced narrowing of practically all joint spaces, with the exception of the terminal interphalangeal joints of the fingers. Areas of subchondral bone destruction and subchondral condensation are demonstrable. Pseudocysts are present in both humeri where there is considerable loss of bone substance.

The electrophoretic distributions of proteins in serum are shown. (Figs. 2, 3 and Table IA.)

Synovial fluid alterations are recorded in Table II.

Arthrotomy of the left knee, through an approach medial and proximal to the patella, with biopsy of the synovial membrane was performed four days before the administration of ACTH. At the time of operation the parietal synovialis appeared pale blue, sclerotic and avascular. The visceral synovialis was darker in color, thicker and less pliable than the parietal synovialis and also less vascular than

normal. The undersurface of the patella was covered with pale avascular granulation tissue. Microscopic examination of the synovialis showed changes characteristic of rheumatoid arthritis.

The effects of ACTH—favorable and adverse—were many. The following changes,

TABLE II
SYNOVIAL FLUID FINDINGS—ACTH EXPERIMENT

Day of ACTH	Amount (cc.)	White Blood Cell Count	Red Blood Cell Count	Poly-morpho-nuclears (per cent)	Sugar Difference* (mg. per 100 cc.)	Mucin Precipitate	Viscosity at 38°
0	6	15,750	128,750	76	..	Fair	13.4
0	6	10,200	6,180	41	31	Fair	19.5
17	2	350	23,900	21	26	Good	290.0
43	2	250	25,250	10	13	Good	371.9
65	2	100	17,900	4	8	Excellent	130.7
96	1	100	10,800	20	11	Excellent	326.4
110	2	200	96,250	44	..	Excellent	6080.0
121	2	800	1,140,000	4	-6	Excellent	92.5
Post-ACTH							
2	0.5	1,500	440,000	4	..	Excellent	741.0
17	14.0	2,200	23,600	2	3	Excellent	30.3
31	5.0	2,200	34,350	7	8	Excellent	37.6

* Represents the difference between serum and synovial fluid sugar concentrations.

in chronologic sequence, will be described: (1) Changes in the clinical manifestations of rheumatoid arthritis, (2) changes in the laboratory manifestations of rheumatoid arthritis, (3) observations relating to adrenocortical function, and metabolic and biochemical effects attributable to ACTH.

The dose of ACTH, initially, was 100 mg. daily in four divided doses. (Fig. 2.) There was no symptomatic improvement until the sixth day, at which time various joints were less tender. By the tenth day she felt "the best in one and one-half years." The changes at that time can be summarized as follows: Feeling of well-being, increase in strength and appetite, absence of morning stiffness, absence of pain on performance of exercises and weight-bearing, increased motion in knees and shoulders, decrease in soft tissue swelling of both knees. Improvement of the same general nature continued during the next ten days. (Fig. 2.) Beginning on about the twentieth day and clearly apparent on the twenty-seventh day of

ACTH, there was an unexpected increase in extension, passive but not active, of the proximal interphalangeal joints. Interestingly, little change occurred otherwise in these joints, as only minimal stiffness, swelling and tenderness were present prior to the

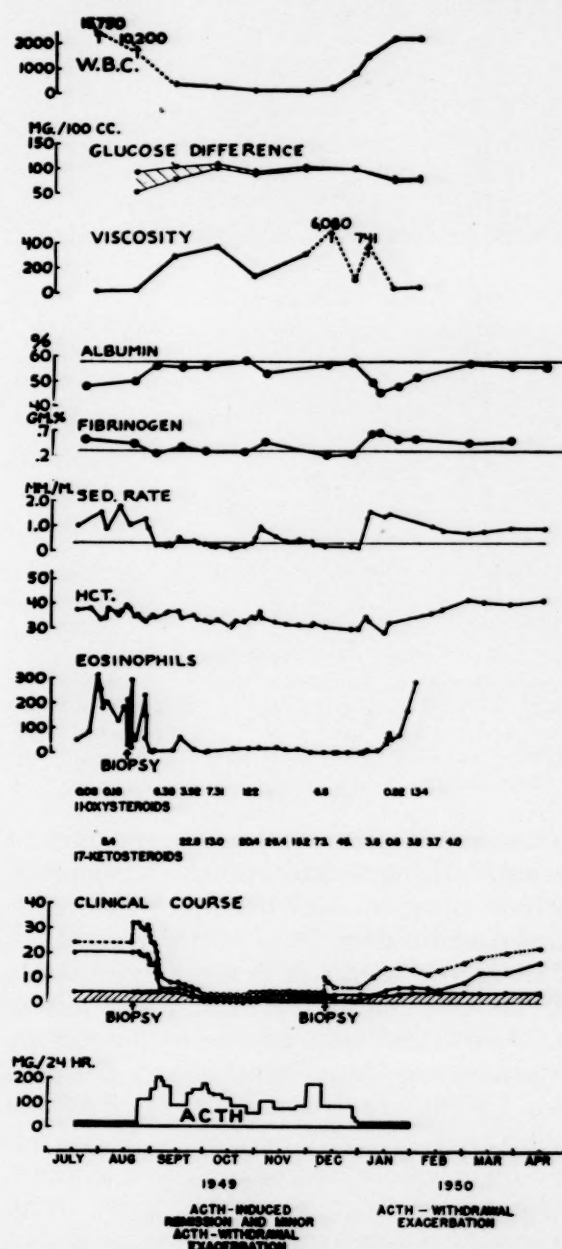


FIG. 2. Graphic representation of clinical course, hemoglobin, hematocrit, sedimentation rate and distribution of proteins determined electrophoretically during and following period of ACTH therapy.

administration of ACTH. (Figs. 4A and 4B.) On the right side passive extension of the

proximal interphalangeal joints had increased from a limitation of 45 to 70 degrees to 5 to 10 degrees and on the left from 30 to 80 degrees to 5 to 15 degrees. During the next thirty-seven days there was little additional change in the articulations, save

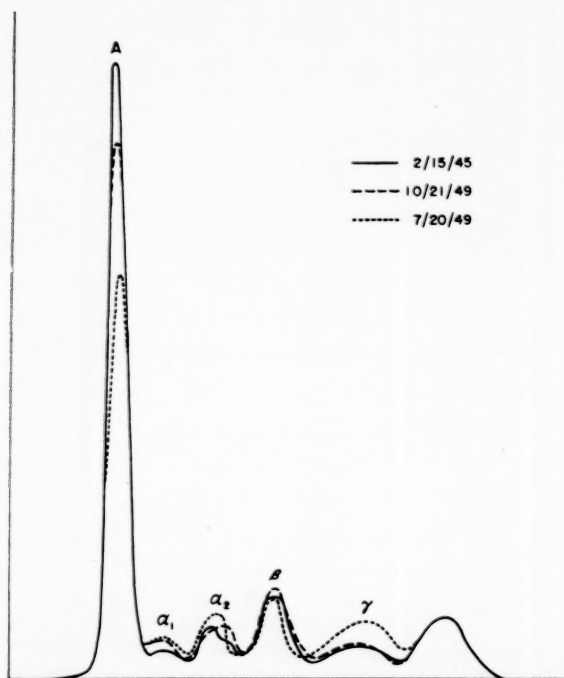


FIG. 3. Electrophoretic patterns of 1.87 per cent solutions of serum in sodium diethyl-barbiturate buffer of pH 8.55 and ionic strength 0.1 after 12,600 seconds at 5.3 volts per cm.

for continued gain in function and muscle strength, owing apparently to the vigorous exercise program which her state of well-being and freedom from pain permitted. A mild flare-up occurred on the sixty-fifth day due to the inadvertent administration of ACTH of low potency, with a resulting drop in dosage from 75 to 42 mg. per day. (Fig. 2.) This exacerbation—the first ACTH withdrawal exacerbation—was characterized by gradually increasing pain, stiffness, swelling and fluid in the left knee. With increase in dosage (to 75 mg.) the symptoms subsided in three or four days but the objective signs were slow to regress. Accordingly, the dose of ACTH was doubled to 150 mg. daily on the ninety-ninth day with the hope of obtaining maximal improvement prior to the second biopsy.

Arthrotomy of the left knee, this time through an approach lateral and proximal to the patella, was performed on the 110th day, at which time the left knee was still the site of slight tenderness, moderate soft tissue swelling and a small effusion.

The parietal synovialis again appeared avascular but was now quite pliable. The visceral synovialis was unchanged. There were no adhesions. No pannus was seen. The articular cartilage of the patella was white, firm and granular. Firm, avascular tissue had apparently replaced the granulation tissue previously present on the undersurface of the patella. Representative specimens of synovialis and a portion of the old healed skin scar were biopsied. The surgeon described the gross appearance as "typical of burned-out rheumatoid arthritis but with less thickening and less fibrosis." Microscopic examination revealed slight synovitis.

Motion in the immediate postoperative period was remarkably easy and painless. Healing proceeded in a normal fashion although the scar showed slightly more keloidal change than did the first.

A severe psychosis appearing on the 130th day necessitated immediate withdrawal of ACTH. The original plan of the experiment included transfer to the metabolic ward for control balance studies, then gradual withdrawal of ACTH, with a view to observing the effects of ACTH withdrawal. The details of the psychosis will be described later.

Objective signs of an ACTH withdrawal exacerbation were evident on the twelfth post-ACTH day with swelling and fluid in the left knee. The patient's mental attitude made impossible careful comparison of the first and second ACTH withdrawal exacerbations. During the next two weeks the flare-up subsided to a large extent.

The patient was discharged to home and clinic care on the thirty-third post-ACTH day. Clinical manifestations of active disease were present but the level of activity was lower than prior to the administration of ACTH. (Fig. 2.) Symptoms were minimal and only the left knee exhibited moderate soft tissue swelling and a slight effusion.

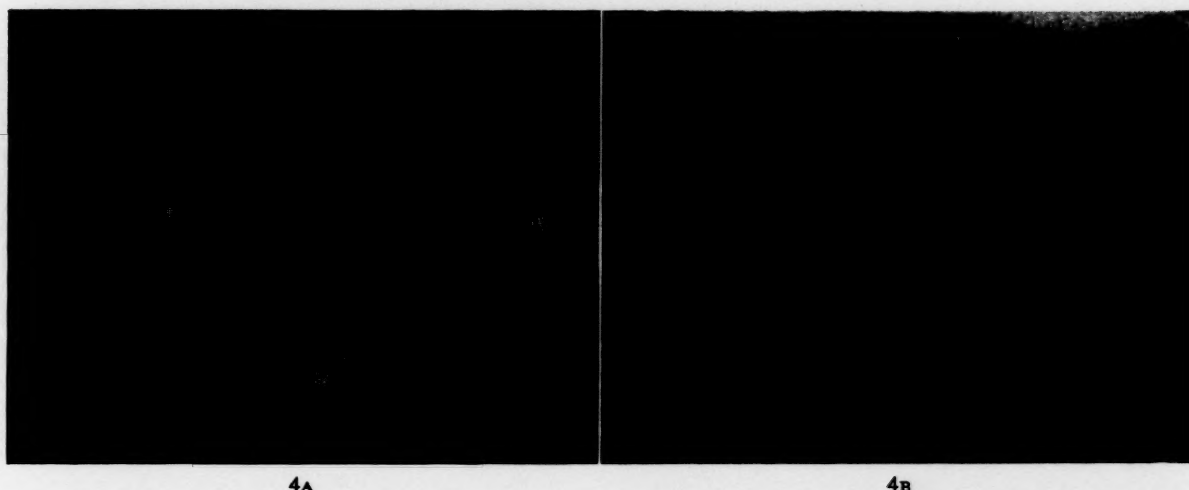


FIG. 4. Flexion deformities of fingers (A) before ACTH; (B) on 124th day of ACTH treatment.

She had gained impressively in functional capacity, apparently as a consequence of decreased pain in the knees and increase in muscle strength. Two presumed extra-articular manifestations of rheumatoid arthritis, namely, hyperhidrosis of hands and feet and minor generalized lymphadenopathy, were not influenced at all by the administration of ACTH.

Joint examination at the time of discharge: Spine: normal. Shoulders: normal. Elbows: permanent flexion of 80 degrees and further flexion to 120 degrees on the right; permanent flexion of 80 degrees and further flexion to 110 degrees on the left. Supination moderately restricted on the left side. Wrists: extension 45 degrees, flexion 50 degrees on the right; extension 5 degrees, flexion 60 degrees, moderate radial deviation on the left. Metacarpophalangeal joints lacked 10 to 20 degrees of full extension and flexion; minimal swelling and no tenderness. Proximal interphalangeal joints: permanent flexion of 30 to 80 degrees with active extension, 5 to 30 degrees with passive extension. Terminal interphalangeal joints: hyperextension of 20 to 30 degrees. Fists incomplete and grips fair. Hips: normal. Straight leg raising: excellent. Knees: full, painless motion with minimal soft tissue swelling on the right; moderate soft tissue swelling, slight effusion and slight limitation of flexion on the left. Ankles: flexion to 30 degrees. Metatarsophalangeal joints: slight limitation of motion and slight tenderness. She was able to rise unaided from a sitting position and could walk, with difficulty, without the help of crutches.

APRIL, 1951



FIG. 5. Flexion deformities of fingers and swelling of proximal phalangeal joints eighty-four days after cessation of ACTH therapy.

Subsequently, there has been gradual return of articular symptoms and signs. On the ninetieth post-ACTH day* the total objective signs closely approximated the pre-ACTH level. (Fig. 2.) Some joints, for example the right knee, exhibited less evidence of soft tissue swelling; others, for example the proximal interphalangeal joints, decidedly more. (Fig. 5.)

* Subsequently there was a decrease in joint symptoms and signs until the 165th post-ACTH day when only slight pain and stiffness in hands and knees persisted. The sedimentation rate at that time was 0.93 mm. per minute, the hematocrit 36 and the hemoglobin 12.6 gm. per 100 cc. However, on the 275th post-ACTH day, after an acute otitis media, joint pain and swelling recurred and have persisted. When examined on the 379th post-ACTH day, she complained of moderate pain and stiffness in hands and both knees. The left knee showed a minimal effusion, the right a moderate effusion. The sedimentation rate was 1.45 mm. per minute, the hematocrit 35.5 and the hemoglobin 11.4 gm. per 100 cc.

The laboratory tests used to assess activity of disease included hemoglobin, hematocrit, sedimentation rate, electrophoretic distribution of proteins in serum, synovial fluid examination and Congo red test. The observations are charted (Fig. 2 and Table II and other tables in text) and require only brief comment.

The hemoglobin and hematocrit declined progressively during the ACTH period. Concurrently, the serum specific gravity (interpreted as a measure of plasma volume) remained constant. An appreciable volume of blood was withdrawn for biochemical determinations; there was no other source of blood loss. Sternal marrow aspirated on the 120th ACTH day revealed absence of stored hemosiderin. This observation confirmed the impression that iron deficiency played the major role in the anemia. During the next ten days ferrous sulfate (0.8 gm. per day) and ACTH were administered concurrently without appreciable hematologic response. However, the subsequent rise in hematocrit with continued administration of ferrous sulfate indicates that iron deficiency was indeed the etiologic factor involved. (Fig. 2.)

Changes in the sedimentation rate paralleled closely the clinical changes. (Fig. 2.) Indeed, the sedimentation rate changes always preceded alterations in the clinical manifestations of disease. For example, during the first six days of complete ACTH withdrawal—at a time when objective signs were negligible—the sedimentation rate increased from 0.1 to 1.24 mm. per minute (Rourke-Ernstene method).

The rapidity with which the serum protein fractions were altered was remarkable. The abnormalities characteristic of active rheumatoid arthritis, that is, increase in alpha-1, alpha-2 and gamma globulin and fibrinogen fractions and decrease in albumin fraction were present before ACTH. (Fig. 1.) Nine days after ACTH there was a moderate decrease in the globulin fractions and a striking decrease in the fibrinogen fraction and a marked increase in the albumin fraction. (Fig. 1.) The greatest

improvement in the protein fractions occurred just prior to the first ACTH withdrawal exacerbation. Comparably rapid reciprocal changes occurred with each ACTH withdrawal exacerbation. Electrophoretic analyses of serum eleven days after the first, and seven days after the second, ACTH withdrawal exacerbation showed increase in the alpha-1, alpha-2 and gamma globulin and fibrinogen fractions and reduction in the albumin fraction. (Fig. 1.) These alterations paralleled closely changes in the sedimentation rate. The fibrinogen fraction showed the greatest change.

The abnormalities in the synovial fluid, namely, volume, nucleated cell counts and differential, character of the mucin and serum-fluid glucose difference became normal. (Fig. 2.) Distinctly unusual increases in viscosity occurred with figures as high as 6,080. Such extremely viscid fluid is never observed normally and suggests either retardation of enzymatic degradation or enhancement of enzymatic synthesis of synovial mucin. Quite striking also was the rapidity with which the viscosity decreased with the two ACTH withdrawal exacerbations. (Fig. 2.) On the first occasion the viscosity decreased in two days from a figure probably well over 350 to 130.7. On the second occasion the viscosity decreased from 741 to 30.3 in thirteen days. The reaction incident to the biopsy also caused marked reduction in the viscosity. It is of interest that the white blood cell count, the character of the mucin and the serum-fluid glucose difference did not change significantly at these times. Changes in the viscosity reflected the trend of events promptly and accurately.

Changes in the Congo red test were minor and not significant.

The observations relating to adrenocortical function include the quantitative eosinophil count and the quantitative urinary excretion of 17-ketosteroids and 11-oxycorticosteroids. These studies are useful in determining the degree of adrenocortical stimulation from a given dose of ACTH.⁹

The stress of operation and the adminis-

tration of ACTH caused marked reduction in the number of circulating eosinophils; continued administration of ACTH, virtual disappearance of these cells. (Fig. 2.) Neither of the two ACTH withdrawal exacerbations was closely correlated with a rise in circulating eosinophils.

The 17-ketosteroid excretion varied greatly during the ACTH period.* (Fig. 2.) The wide fluctuations are unexplained. Quite consistent, however, were the very low values obtained in the immediate post-ACTH period. Within seven days, during which time the eosinophil count was 0, the excretion of 17-ketosteroids decreased from 45 mg. or more to 3.6 mg. per twenty-four hours. Subsequent determinations were even lower and have remained low (4.0 mg. per twenty-four hours or less).

The 11-oxycorticosteroid excretion increased following institution of ACTH therapy. (Fig. 2.) The low potency of the ACTH producing the first ACTH withdrawal exacerbation was reflected clearly in decreased 11-oxycorticosteroid excretion.

In this case there was no delineation between the physiologic or metabolic effects of ACTH and the so-called adverse or side-effects. This is understandable as long-continued administration of large doses of ACTH leads to predictable and largely undesirable metabolic effects which closely simulate Cushing's syndrome.

The adverse metabolic effects of ACTH were soon apparent. Within the first two or three weeks of ACTH "moon facies," pigmentation of the face and creases of the palms, increased hair growth, acne, thickening of the skin and recession of the temporal hairline appeared. (Figs. 6 and 7.) Toward the end of the ACTH period the altered appearance was striking and included the "buffalo-hump" and moderate alopecia. In addition, subcutaneous tissues throughout the body became quite tender and three striae appeared on the inner aspects of

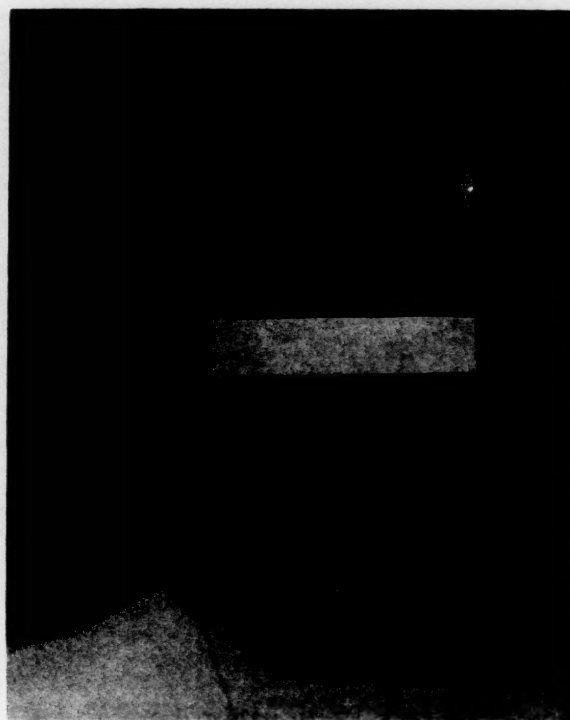


FIG. 6. Photograph of face before ACTH.

both upper arms, adjacent to the axillary folds.

Furunculosis of the axillary regions, with surrounding cellulitis, was a recurrent and troublesome problem. This cannot be attributed directly to ACTH, as numerous furuncles were present in the buttocks prior to the ACTH period. It is of interest that the local and systemic manifestations of these infections were not modified by ACTH.

ACTH withdrawal caused regression of most of these adverse effects. Improvement was apparent in about three weeks and progressed rapidly with complete disappearance of these signs in approximately four months except for the striae, slight acne, recession of the temporal hairline and slight alopecia which persist to the time of this writing (165 days post-ACTH).

ACTH had a prompt effect on the menses. Menstruation occurred on the third ACTH day but this period was abnormally scanty. This was followed with amenorrhea during the entire ACTH period and for fifty days post-ACTH. The menstrual periods in the post-ACTH period have been characterized

* We wish to thank Dr. Fuller Albright and his group for their generous cooperation in making possible the determinations of the 17-ketosteroid and 11-oxycorticosteroid excretions.

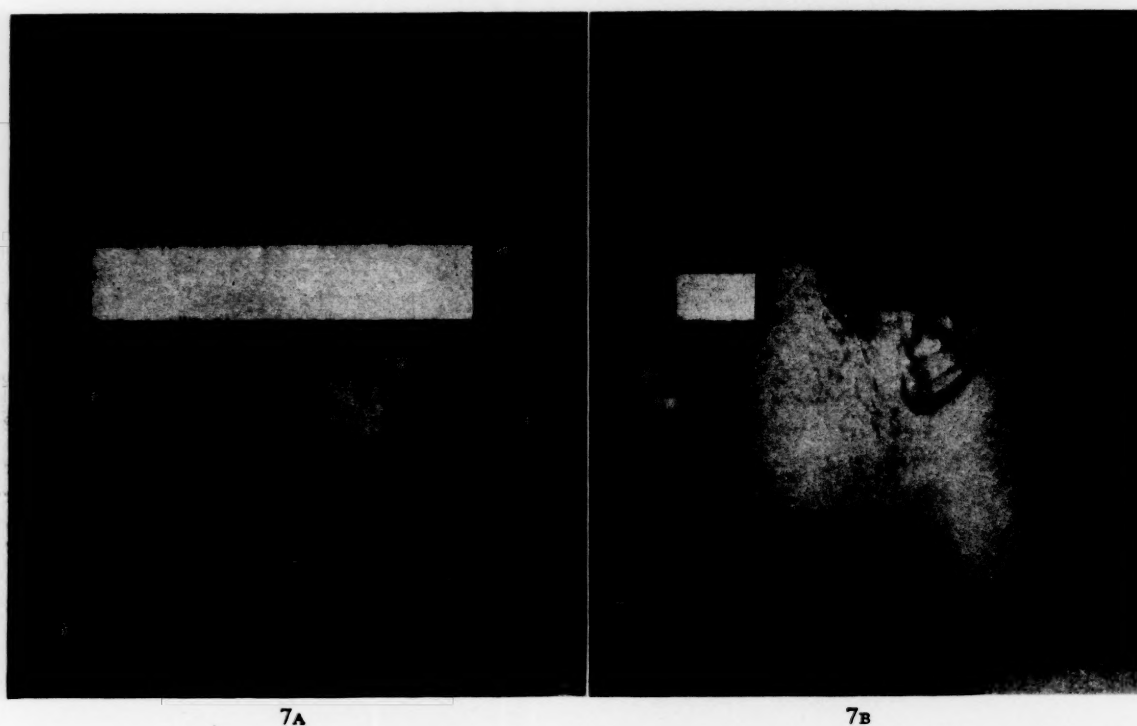


FIG. 7. A and B, photograph of face on 124th day of ACTH treatment, showing moon-like facies, hirsutism, pigmentation and acne and recession of hair.

by scanty flow. Studies relating to the cessation of menses were inconclusive. The follicle-stimulating hormone and estrin excretions were within normal limits. It is possible that androgenic steroids were inhibiting the effect of estrin on the endometrium.

The observed alterations in carbohydrate metabolism were relatively slight. (Table III.) Slight insulin resistance was recorded on the twenty-ninth ACTH day. Up to the 100th ACTH day postprandial hyperglycemia was occasionally noted. Between the 100th and the 110th day, coincident with increase in the dose of ACTH, postprandial hyperglycemia, slight glycosuria and moderate insulin-resistance developed. ACTH withdrawal promptly reversed this abnormal trend; the glucose-tolerance test on the twenty-third and the insulin-tolerance test on the twenty-ninth post-ACTH day were normal.

The increase in blood pressure was likewise relatively slight. Pre-ACTH blood pressure determinations averaged 120/70. During the last 100 days of ACTH the blood pressure was rarely less than 140/90

and occasionally 150/100. Post-ACTH pressures have ranged between 120 to 130 systolic and 70 to 80 diastolic.

As was expected the administration of ACTH altered significantly the electrolyte and water equilibrium. (Fig. 8.) Alkalosis developed gradually on two occasions between the tenth and sixtieth ACTH day and between the 100th and 130th day. Gain in weight was gradual during the first seventy days (seven pounds) but rapid (eight pounds) during the next fifteen days. The sudden increase in weight was unaccompanied with changes in the concentration of serum electrolytes or the specific gravity of the serum. Restriction of sodium during the remaining forty-five days of ACTH administration resulted in gradual loss of weight (ten pounds).

Although unequivocal signs of potassium deficiency did not appear at any time, the serum levels and the abnormalities in the electrocardiogram suggested potassium depletion. The serum potassium values and the electrocardiograms were normal until the 110th ACTH day, at which time a drop

in serum potassium (to 3.3 mEq./L.) coincided with lowering and inversion of the T waves. Intravenous infusion of 30 mEq. of potassium restored the T waves to normal, but the changes in the serum potassium values were slight (to 3.8 mEq./L.). On the

TABLE III
CARBOHYDRATE METABOLISM ALTERATIONS

Minutes:	Insulin Tolerance Test						
	0	20	30	45	60	90	120
Date	mg./100 cc.						
Before ACTH.....	98	80	68	90	107	119	119
29th ACTH day.....	129	96	95	95	99	122	133
78th ACTH day.....	142	104	96	94	100	101	111
30th Post-ACTH day.....	86	62	43	63	85	85	90

Minutes:	Glucose Tolerance Test				
	0	30	60	120	180
Date	mg./100 cc.				
Before ACTH.....	100	155	123	129	101
22nd ACTH day.....	92	136	132	97	79
24th Post-ACTH day.....	91	131	141	85	92

Date	Serum Glucose Levels	
	Fast-ing	Two Hours Post-prandial
	mg./100 cc.	
Before ACTH.....	...	104
45th ACTH day.....	108	171
59th ACTH day.....	104	134
66th ACTH day.....	96	150
74th ACTH day.....	81	131
87th ACTH day.....	111	202
102nd ACTH day.....	162	174
108th ACTH day.....	138	219
116th ACTH day.....	125	178
122nd ACTH day.....	136	221
1st Post-ACTH day.....	100	133
4th Post-ACTH day.....	124	...

121st ACTH day the T waves again became inverted and the serum potassium value was 2.6 mEq./L. This time orally administered potassium chloride (4 gm. daily) reversed the abnormal trend. On the 130th day,

when the patient was exhibiting serious psychotic behavior, the T waves became inverted for the third time. Although potassium chloride had been given orally for nine days and the serum potassium value was normal (4.3 mEq./L.), potassium

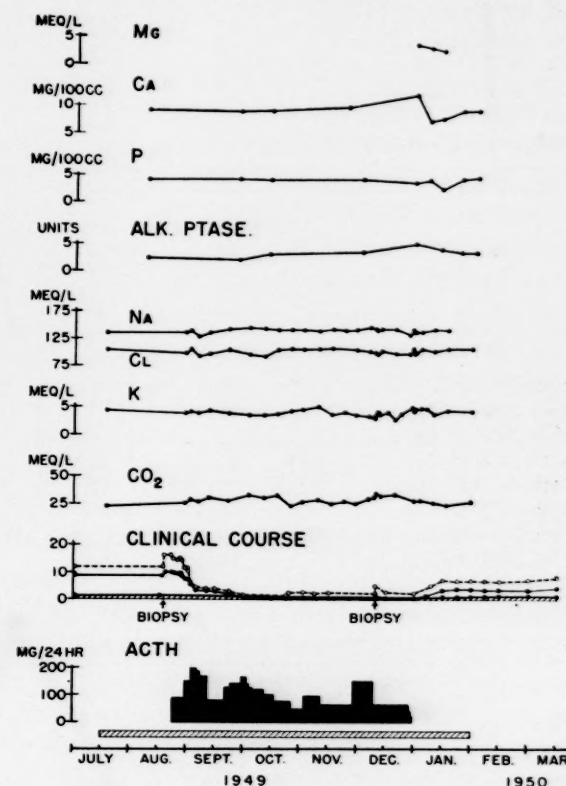


FIG. 8. Graphic presentation of the alterations in serum electrolytes during the course of ACTH therapy.

depletion could not be ruled out as a factor contributing to the psychosis. Consequently, an infusion containing 90 mEq. of potassium was given, in addition to the oral potassium chloride. Ten minutes after the infusion the electrocardiogram was normal and the serum potassium was 4.8 mEq./L. without any alteration in her psychosis. Sodium restriction and oral potassium chloride were continued for several days post-ACTH. No further abnormalities in the serum electrolytes or electrocardiogram were noted.

During the course of this study many of the laboratory procedures which have been used by this Clinic for the study of rheumatoid arthritis were repeated in this case in an effort to learn more about the changes induced by ACTH.

TABLE IV
LIVER FUNCTION TESTS

Date	Van den Bergh (mg./100 cc.)	Bromsulfalein Retention (Per cent)	
Before ACTH	0.3/0.4	5'	15'
29th ACTH day	<0.2/0.3	40	4
49th ACTH day	0.2/0.5
101st ACTH day	..	32	6
9th Post-ACTH day	0.4/0.4	52	12
16th Post-ACTH day	..	27	67
22nd Post-ACTH day

Date	Prothrombin Seconds	Cephalin Flocculation		Thymol Flocculation	Thymol Turbidity Units	Cholesterol	Cholesterol Esters
		24 Hr.	48 Hr.				
Before ACTH	16/15	1+	1+	2+	3	182	94
26th ACTH day	13/15
35th ACTH day	..	2+	3+	0	2.5
49th ACTH day	17/18	2+	3+	0	1.5	193	121
74th ACTH day	18/18	2+	3+	1+	2.5	185	122
100th ACTH day	19/18	2+	3+	3+	2.5	178	94
9th Post-ACTH day	..	±	1+	..	1.5	160	45
17th Post-ACTH day	19/18	238	178
34th Post-ACTH day	240	150
86th Post-ACTH day	199	120

Minutes:	Galactose Tolerance Test			
	Intravenous		Oral	
	60	75	30	60
Date	(mg./100 cc.)		(mg./100 cc.)	
Before ACTH	0	0	22	30
23rd ACTH day	68	42
36th ACTH day	5	3
72nd ACTH day	0	0
34th Post-ACTH day	40	40

Date	Non-protein Nitrogen (mg./100 cc.)	Uric Acid
Before ACTH	24	2.7
35th ACTH day	29	2.8
59th ACTH day	23	2.3
7th Post-ACTH day	20	..
10th Post-ACTH day	17	3.6
35th Post-ACTH day	16	..

Calcium Excretion in Urine gm./24 hr.	
Before ACTH	0.252
23rd ACTH day	0.208
100th ACTH day	0.127

The observations are tabulated. Although the interpretations are not clear, certain of the changes must be attributed to ACTH and will be mentioned briefly. Many of the tests commonly used to assess hepatic function were performed. Borderline or abnormal values in one or more of these tests are often seen in patients with rheumatoid arthritis.¹⁰ In this case the pre-ACTH studies were normal, save for the direct bilirubin (0.3 mg. per 100 cc.). During the latter half of the ACTH period the cephalin flocculation and bromsulfalein tests became abnormal. The observed alteration in hepatic function cannot be ascribed to the state of the disease, and the explanation is not apparent. There was no significant change in calcium, phosphorus and phosphatase until the 130th day when, concurrently with the psychosis, the calcium and phosphorus rose to abnormal values (12 and 5 mg. per 100 cc., respectively.) (Fig. 8.) Subsequent calcium values were low (7.3 and 7.6 mg. per 100 cc.) and later normal. The changes observed in the oral galactose tolerance test are inexplicable. Early in the ACTH period galactose blood levels were high thirty and sixty minutes after ingestion of the sugar. Since the intravenous galactose tolerance was normal, the high levels were presumably due to abnormally rapid absorption rather than impaired utilization of galactose. Later the blood was cleared completely of galactose, and still later the blood levels were in the borderline range. These alterations in oral galactose tolerance tests could not be correlated with changes in thyroid or hepatic function. Lastly, there was a late change in the cholesterol ester-cholesterol ratio. From a range between 50 and 65 per cent, the ratio suddenly decreased to 28 per cent (cholesterol 160 mg. per 100 cc., cholesterol esters 45 mg. per 100 cc.). In the immediate post-ACTH period the ratio increased once more to 60 per cent. It is not clear whether the change reflected increased adrenocortical activity or impairment of hepatic function. (Table iv.)

The acute psychosis was the most serious complication and necessitated termination

of the experiment on the 130th day. During the last thirty days of ACTH the patient's attitude changed from one of hopefulness and cooperation to one of moody, suspicious preoccupation. The principal preoccupation was with the marked changes in physiogomy produced by ACTH and with the probability of a post-ACTH relapse. During the last three days of ACTH she exhibited agitated, aggressive behavior on several occasions. In the intervals she was quite rational and had intense feelings of guilt and fears of insanity. On the last day of ACTH, and for five days thereafter, she was seriously and unquestionably psychotic. Initially, the striking features were periods of agitated behavior, stereotyped speech, marked negativism and urinary incontinence. The content of her speech had reference to her changed appearance, fear of insanity and of impending doom. Later, depressive features were more prominent. On the seventh post-ACTH day she regained interest in her surroundings and related her fears in a coherent and seemingly logical fashion. On the twelfth day objective evidence of an ACTH withdrawal exacerbation was apparent but she denied all types of muscular, articular and constitutional symptoms. Her mental status was normal at the time of discharge (thirty-three days post-ACTH) and has remained so. As mentioned previously the electrocardiograms at the onset of the psychosis were consistent with intracellular potassium depletion. In the absence of accurate determinations of tissue electrolytes it is impossible to say what role disturbances in electrolyte equilibrium played in the mental aberration. The improvement did not seem to be related directly to the administration of potassium salts.

Basal electroencephalograms were done before and during the administration of ACTH. The first of these, August 8, 1949, was interpreted as a normal record. The one taken on October 19, 1949, was likewise normal except for slow activity at the vertex. Comparison of the electroencephalogram taken on November 3, 1949, with the pre-

ceding records revealed slight differences; paroxysmal bursts of slow activity at the vertex and decrease of the occipital alpha activity, both voltage and number of waves. Unfortunately, we were unsuccessful in our attempts to obtain a satisfactory tracing during the psychosis.

As regards the etiologic factors involved in this psychosis as well as in psychiatric disturbances which have occurred in other patients with rheumatoid arthritis undergoing ACTH therapy, one cannot as yet assay the relative importance of the possible ACTH-induced, cerebral metabolic changes referred to before as opposed to psychogenic factors. The latter may center about the response of the patient to the therapeutic effects of ACTH. If these are such as to involve for the patient a rather abrupt psychologic and social adaptation from the chronic dependency of bed-chair invalidism to a relatively active, competent life, considerable emotional stress may be incurred in the process. If, moreover, as in this case, the incapacitating disease is one with probable psychosomatic characteristics, dramatic changes in physical status may have particular impact upon the underlying personality structure and in fact precipitate a breakdown of the previous psychic integration. These latter factors must certainly be considered in the mental disturbances which occurred in this patient.

COMMENTS

The varying life cycle^{1,11,12} of rheumatoid arthritis during a seven-year period is well exemplified by this patient. The disease process, as measured by subjective complaints, objective signs and laboratory abnormalities, was active and progressive for about two years. Gradually the constitutional and articular symptoms abated, the objective signs subsided and the laboratory criteria of active disease disappeared. At the peak of the remission there were no constitutional or articular symptoms; the only objective signs consisted of slight thickening of the soft tissues about the knee joints and fixed deformities of the elbow joints; and the sedimentation rate was

normal. In short, all the criteria necessary to justify the use of the term "remission" were present. The disease in this case, then, followed the favorable course observed in approximately 15 per cent of patients with rheumatoid arthritis receiving simple medical measures.¹

The early part of this study showed a close correlation between the clinical manifestations and the protein fractions as determined electrophoretically. As previously mentioned, active disease was characterized by an increase in the alpha-1, alpha-2 and gamma globulin and fibrinogen fractions and a marked reduction in the albumin fraction; spontaneous remission by reciprocal changes. The electrophoretic analyses done in this clinic have not shown the T component described by others.¹³ One of the earliest signs of remission was a rise in the albumin fraction. Complete restoration of the protein fractions to normal was the outstanding laboratory feature of the spontaneous remission. Indeed, the albumin fraction was higher and the alpha-1 and alpha-2 and fibrinogen fractions lower than at the peak of the ACTH remission. The tendency for the gamma globulin to decrease below normal values during remission is unexplained but has been observed in other patients.⁷

In spite of these clinical and laboratory evidences of remission the disease process was still active, as shown by the persistence of moderate synovitis. The synovial membrane, obtained from the left elbow joint eighteen months after the onset of the natural remission, showed complex histologic changes. (Fig. 9.) (At this time the sedimentation rate had risen slightly above normal.) In general, it was fibrotic and contained few inflammatory cells. In some areas, however, it was infiltrated by a fibrin-like material and the adjacent tissues showed slight edema and fixed cell activity, as well as scattered lymphocytes, histiocytes and rare polymorphonuclears. The over-all picture was in keeping with mild focal activity rather than complete abeyance of the disease process. Synovial tissue removed from patients who have experienced and

maintained more complete remissions is not available to determine whether histologic evidence of synovitis persists in such cases.

The three-year unremitting course following the postoperative exacerbation is unexplained and represents one of the vagaries of this disease. The conservative therapeutic program which seemed helpful in inducing a remission during the initial period with active disease was not effective during the postoperative exacerbation. As previously emphasized,¹ the conservative methods are generally believed to be helpful. However, no proof is available that they alter the natural course of the disease.

The clinical changes during the ACTH-induced remission, allowing for differences in the stage of the disease, were comparable to those observed during the spontaneous remission, except that the changes occurred in weeks instead of many months. As in the spontaneous remission, alteration in the protein pattern was the earliest sign of a favorable trend. The rapid and marked change in the fibrinogen, albumin and gamma globulin fractions is noteworthy. Slowing of the sedimentation rate paralleled these changes. At the peak of the ACTH remission the protein fractions were well within the normal range. However, the alpha-1 and alpha-2 globulin and fibrinogen fractions were higher and the albumin fraction lower than at the peak of the spontaneous remission. Again, the gamma globulin values fell lower than the average normal level.

The changes which occurred in the synovial fluid require no further comment. Suffice it to say that the return to normal was complete but that the increase in viscosity proceeded to a point far beyond that ever observed in normal synovial fluid.

The failure of ACTH, in the absence of iron, to influence the anemia is of interest. Ferrous sulfate was prescribed during the initial period with active disease. As is usually the case the anemia persisted during the active phase and regressed during the spontaneous remission. During the first 120 days of ACTH no ferrous sulfate was given and the anemia progressed. The



FIG. 9. Synovial tissue removed from elbow eighteen months after the onset of the spontaneous remission, the infiltration by fibrin-like substance and the surrounding slight edema and fixed cell activity and the scattered lymphocytes and histiocytes are apparent.

response to ferrous sulfate indicates that iron was essential for improvement of the anemia. This suggests that iron not only was ineffective during the period of active disease but also was not stored for future needs.

The ACTH remission was accompanied also with decrease in the degree of synovitis as judged by the microscopic appearance of synovial membrane biopsied from the same knee joint before and 110 days after ACTH. (Fig. 10.) The pre-ACTH specimens showed varying degrees of intimal hypertrophy and hyperplasia, lymphocytic infiltration, increased mast and plasma cells, perivascular hemosiderin deposits, edema and considerable fibrosis with some fairly cellular areas of "active" fibroblasts. A section of pannus showed all of these changes and, in the vascular and congested subintimal zone, pronounced infiltration of lymphocytes, plasma cells and one "lymphoid nodule." The over-all findings were quite typical of chronic rheumatoid

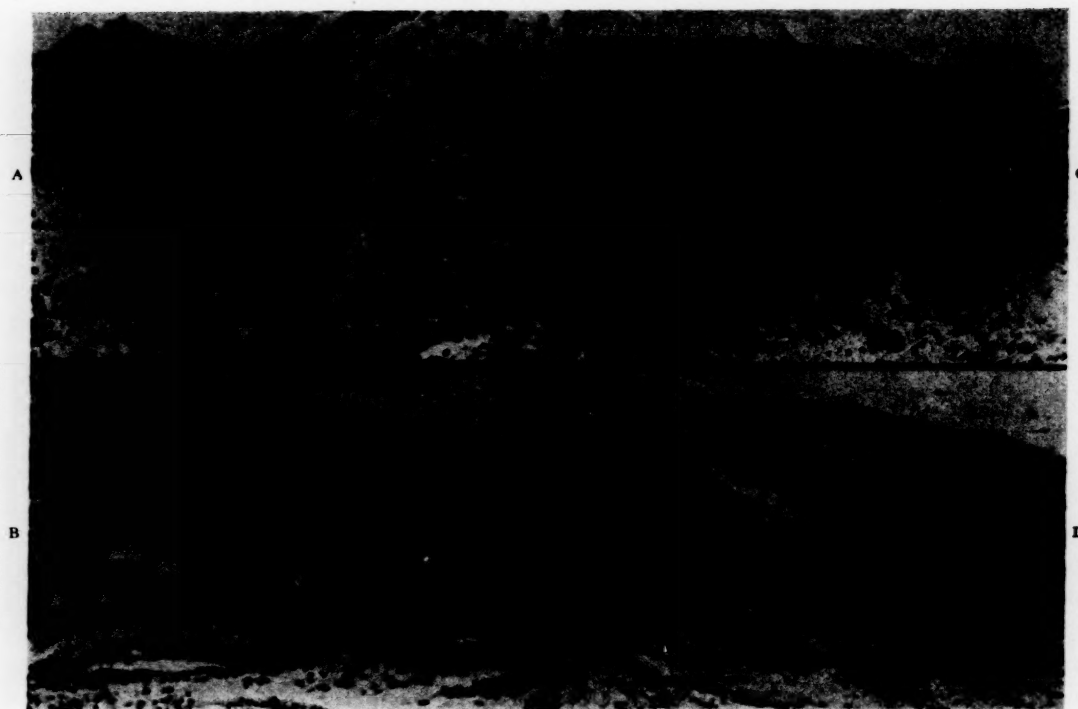


FIG. 10. Synovial tissue removed from left knee (A and B) before ACTH and (C and D) after 110 days of ACTH treatment; (A) and (C) were removed from the visceral surface, (B) and (D) from the parietal surface of the joint. Note reduction in edema and cellular infiltration.

arthritis. Considerable variation was apparent in the several pieces of synovia, indicating the sampling error which must be considered in comparing such biopsies. The histologic changes in the ACTH-remission biopsy corresponded in general to those in the pre-treatment biopsy but were much less pronounced. Hypertrophy and proliferation of synovial lining cells were present in some areas, but in most places the intima was only one cell layer in thickness. Scattered small foci of fibrinoid degeneration were found on the synovial surface. Lymphocytic infiltration was slight, almost entirely perivascular and no lymphoid nodules were seen. Mast cells were less numerous and plasma cells were rare or absent. The fibrous tissue seemed denser, more hyaline, less cellular and less vascular. Although the possibility of sampling errors could not be entirely dismissed, it seemed reasonably definite that a considerable reduction in synovial inflammation had occurred since the previous biopsy. The most striking change was an essential absence of edema and, apparently, a dense interstitial fibrosis which seemed to have

replaced some of the inflammatory exudate. Nevertheless, there was present still a moderate perivascular lymphocytic infiltration and continued evidence of focal synovial degeneration with fragmentation and sequestration of collagen, atrophy and pyknosis of fibroblasts, interstitial fibrinoid change and absence of a surface layer of synoviocytes. It was difficult to compare this biopsy with that obtained at the peak of the spontaneous remission, owing to the paucity of synovial membrane from the latter operation. In both, however, there was mild focal inflammatory activity, slight in the post-ACTH specimen, suggesting that there was not complete abeyance of the disease process.

It might be mentioned that the scar resulting from the two arthrotomies showed some keloid formation. At the second operation the first incisional scar was biopsied. It showed some keloidal hyperplasia but this was not clearly beyond the limits of normal.

During the ACTH-remission a reduction in the inflammatory changes in muscles also occurred as shown by the histologic

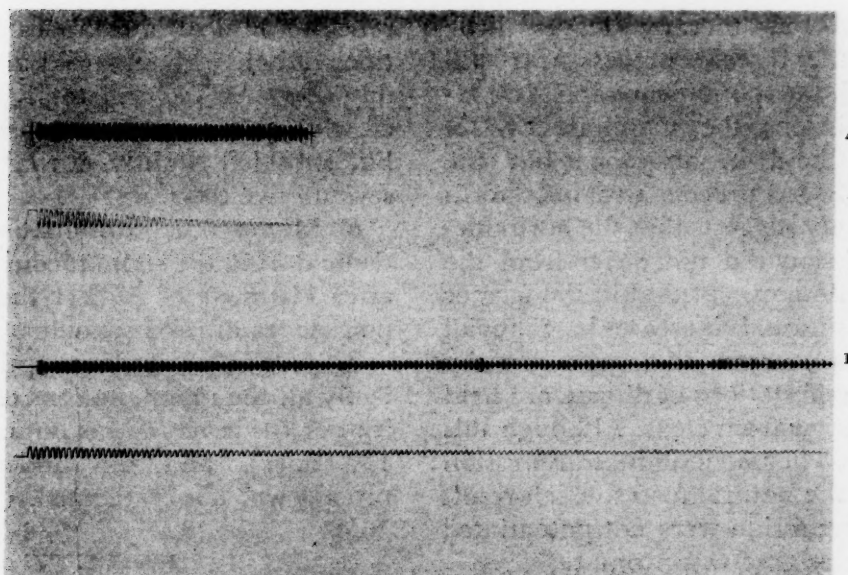


FIG. 11. Simultaneous electromyograms and ergograms using anterior tibial muscles while patient dorsiflexed foot moving a ten-pound weight a distance of 8 inches; (A) before ACTH, at which time only forty-nine contractions could be performed, (B) after thirty-two days of ACTH treatment when 157 contractions were performed.

findings in muscle biopsied before and 110 days after ACTH. In the specimen obtained before treatment numerous small perivascular foci of mononuclear cells, chiefly lymphocytes, were seen in the endomysium and an occasional small focus in the perimysium. Some muscle fibers were thin with relative increase in sarcolemmal nuclei. Moderate atrophy was present. In the post-ACTH biopsy no inflammatory foci were found in the muscle. It is impossible to determine whether this is due to chance variation such as that encountered with repeated muscle biopsies in any patient with rheumatoid arthritis or due to complete disappearance of muscle inflammation. Some muscle fibers were basophilic with clusters of sarcolemmal nuclei in relation to them. The specimen presented a picture of moderate atrophy with a question of regeneration.

Clinical evidence of increased muscle strength and endurance during the ACTH remission was corroborated by electromyographic and ergographic findings. (Fig. 11.) Tracings obtained from the anterior tibial muscles on the thirty-second day of ACTH treatment showed an increase in contractions from the pre-ACTH level of forty-nine to 157.

The adverse effects attributable to ACTH occurred early and increased progressively during the course of treatment, culminating in a severe psychosis. With long-continued administration of large doses of ACTH it is not possible to separate the "therapeutic" from the "toxic" effects. All of the available criteria of adrenocortical function indicate that the individual with rheumatoid arthritis has normally functioning and responsive adrenal glands.¹⁴ Presumably, ACTH modifies the disease process by stimulating normal adrenal glands. Hence, the therapeutic effect and the metabolic effects of hyperadrenocorticism go hand in hand. It would seem that the favorable and unfavorable effects of ACTH in the doses administered can be dissociated only in conditions amenable to short-term treatment.

ACTH withdrawal resulted in exacerbations of moderate severity. Most striking was the rapidity with which the protein fractions, especially albumin and fibrinogen, and the synovial fluid viscosity, were altered. These changes preceded a rise in circulating eosinophils.

The rapid recurrence and persistence of clinical and laboratory manifestations and the persistence of mild synovitis after long-

continued ACTH therapy leaves little doubt that the disease process was still active. In both the spontaneous and ACTH-induced remissions the manifestations of disease were held in abeyance but the underlying disease process was not eradicated. The study suggests that the hormone-induced remission did not differ from the natural remission, except that in the former instance an unusual increase in synovial fluid viscosity occurred. The mechanism by which the manifestations of disease are held in abeyance is far from clear. Although this patient was in a hormone-induced remission for 130 days, the natural forces which result in a natural remission were not potentiated or mobilized; relapse was prompt.

SUMMARY AND CONCLUSIONS

1. The natural course of rheumatoid arthritis is variable and unpredictable. These features of the disease were observed during a seven-year study of a twenty-one year old female with rheumatoid arthritis during an initial period with active disease, a spontaneous remission, a postoperative exacerbation, an ACTH-induced remission and two ACTH withdrawal exacerbations.

2. The periods of active disease were characterized by abnormalities in the serum protein fractions as determined electrophoretically and in the synovial fluid. The protein fractions returned to normal during the spontaneous and ACTH-induced remissions. Serial examination of synovial fluid during the ACTH experiment showed rapid reversal of the abnormalities and an unusual increase in viscosity.

3. The spontaneous and ACTH remissions were comparable, except for the abnormally elevated synovial fluid viscosity and the persistent anemia in the latter instance.

4. The administration of ACTH was accompanied with many undesirable effects, including an acute psychosis. The observations and the implications of long-term ACTH are discussed.

5. Partial and complete ACTH withdrawal were followed promptly by recur-

rence of clinical and laboratory manifestations of active rheumatoid arthritis. Ninety days post-ACTH the total objective signs closely approximated the pre-ACTH level but subsided slightly during the following seventy-five days.

6. Microscopic examination of synovial tissue during the spontaneous remission and after 110 days of ACTH therapy revealed persistence of mild synovitis.

7. ACTH* altered promptly and dramatically all the manifestations of disease activity but the reversal was not complete (after 130 days), and the underlying disease process was not eradicated.

REFERENCES

1. SHORT, C. L. and BAUER, W. The course of rheumatoid arthritis in patients receiving simple medical and orthopedic measures. *New England J. Med.*, 238: 142-148, 1948.
2. BAUER, W. and CLARK, W. S. The systemic manifestations of rheumatoid arthritis. *Tr. A. Am. Physicians*, 66: 339, 1948.
3. HENCH, P. S., KENDALL, E. C., SLOCUMB, C. H. and POLLEY, H. F. The effect of a hormone of the adrenal cortex (17-hydroxy 11-dehydrocorticosterone: Compound E) and of pituitary adrenocorticotrophic hormone on rheumatoid arthritis; preliminary report. *Proc. Staff Meet., Mayo Clin.*, 24: 181, 1949.
4. PERLMANN, G. E. and KAUFMAN, D. Electrophoretic distribution of proteins in serum, plasma and synovial fluid of patients with rheumatoid arthritis. *J. Clin. Investigation*, 25: 931, 1946.
5. ROPES, M. W., ROSSMEISL, E. C. and BAUER, W. The origin and nature of normal human synovial fluid. *J. Clin. Investigation*, 19: 795, 1940.
6. ROPES, M. W. et al. To be published.
7. ROPES, M. W., PERLMANN, G. E. et al. Unpublished data.
8. SHORT, C. L., BECKMAN, W. W. and BAUER, W. Gold therapy in rheumatoid arthritis. *New England J. Med.*, 235: 362, 1946.
9. FORSHAM, P. H., THORN, G. W., PRUNTY, F. T. G. and HILLS, A. G. Clinical studies with pituitary adrenocorticotropin. *J. Clin. Investigation*, 8: 15, 1948.
10. ROPES, M. W. et al. Unpublished data.
11. STEINBROCKER, O. Therapeutic results in rheumatoid arthritis. *J. A. M. A.*, 131: 189, 1946.
12. ROPES, M. W. and BAUER, W. Rheumatoid arthritis: its varied clinical manifestations. *New England J. Med.*, 233: 592-596, 1945.
13. WALLIS, A. D. The serum proteins in rheumatoid arthritis. *Ann. Int. Med.*, 32: 53, 1950.
14. CLARK, W. S. et al. Unpublished data.

* We are indebted to Dr. John R. Mote of the Armour Laboratories, Armour and Company, Chicago, Ill., for the ACTH used in this study.

Rheumatoid Arthritis in the Aged*

RUSSELL L. CECIL, M.D. and WILLIAM H. KAMMERER, M.D.

New York, New York

IT is worthy of comment that there is practically no literature on the subject of rheumatoid arthritis in the aged. Numerous studies have appeared on the subject of rheumatoid arthritis in children, a sub-division of the disease generally referred to as Still's disease or juvenile rheumatoid arthritis. Just why rheumatoid arthritis in the aged has received no attention is difficult to understand. The disease appears frequently enough in individuals past sixty although a majority of cases have their onset in the twenties or thirties, less frequently in the forties or in females at the time of menopause. The only reference which we have been able to discover which treats this topic seriously is an article by Schnell.¹ This author reviewed forty-one cases and all of the patients were over fifty-five years of age. He stresses several characteristics, among them a proclivity for involving the large joints rather than the small joints of the hands or feet, very high sedimentation rates and infrequency of secondary anemia. Schnell thought from his rather superficial study of this group of cases that the prognosis was worse in elderly patients than in those who contracted the disease in the earlier decades of life. Our interest in this topic was aroused several years ago by a reference in a European medical journal to the "benign rheumatoid arthritis" of the aged. Having encountered some rather severe cases of this disease in patients in whom the first symptoms developed after the age of sixty or seventy, we began to wonder if rheumatoid arthritis in the aged had any special features which would differentiate it from the disease in

younger individuals. Hence we present this study which is based on an investigation of 100 consecutive cases of rheumatoid arthritis which developed in patients at or after the age of sixty. These cases have been collected from the files of the Arthritis Clinic at the New York Hospital and from our own private practice.

Sex. The patients in this series were divided equally between the male and female sex. There were exactly fifty patients in each group. This was quite at variance with the usual sex distribution, most writers reporting two to three times as many females as males who become afflicted with the disease. We have no explanation to offer for this apparent change in sex incidence with the advance in years.

Age. Seventy-five of the 100 patients fell between the ages of sixty and seventy at the time of onset of their joint symptoms. Twenty-five had their onset after the age of seventy.

Severity. In classifying our cases with respect to the stage of the disease (Table I) we followed the criteria recommended by the American Rheumatism Association,² which are as follows:

In stage I or the early cases (1) no destructive changes are present roentgenologically. (2) Roentgenologic evidence of osteoporosis may be present.

In stage II or the moderately severe cases (1) roentgenologic evidence of osteoporosis with or without slight subchondral bone destruction, slight cartilage destruction may be present. (2) There are no joint deformities although limitation of joint mobility may be present. (3) There is

* From the Medical Service of the New York Hospital and the Department of Medicine of Cornell University Medical College, New York, N. Y. Read before the Seventh International Congress on Rheumatic Diseases in New York City, June, 1, 1949.

adjacent muscle atrophy. (4) Extra-articular soft tissue lesions such as nodules and tenovaginitis may be present.

In stage III or the severe cases (1) roentgenologic evidence of cartilage and bone destruction exists in addition to osteoporosis.

TABLE I
CLASSIFICATION OF CASES ACCORDING TO SEVERITY

I, Mild	43
II, Moderately severe	47
III, Severe	10
IV, Terminal	0

sis. (2) There is joint deformity such as subluxation, ulnar deviation or hyperextension without fibrous or bony ankylosis. (3) There is extensive muscle atrophy. (4) Extra-articular soft tissue lesions such as nodules and tenovaginitis may be present.

In stage IV or the terminal cases (1) there is fibrous or bony ankylosis, (2) criteria of stage III.

From the figures presented in Table I it will be seen that fifty-seven (over half) of our patients fell into the moderately severe or definitely severe groups; slightly less than half were mild early cases.

Functional Capacity. Twenty-nine patients showed slight or no actual functional incapacity. By this we mean that although one or more joints were swollen, tender and somewhat painful with motion, the range of motion was complete, and the patient was able to carry on most of his usual activities. In seventy-one patients there was moderate or considerable functional disability with limited joint mobility which handicapped them to a greater or less extent in carrying out the duties of their occupation or of self care.

Duration. We have also classified our patients with respect to the duration of the disease. Fifty-five per cent or more than one-half fell into what is usually referred to as early cases, that is, cases of less than one year's duration. This is a considerably higher percentage of early cases than we encountered in a previous study of rheumatoid arthritis of all ages in which only 28 per cent fell into the early group.³ Evidently, elderly patients are more prone to

seek prompt medical aid than the younger patients who are actively engaged in business or in the responsibilities of caring for a family.

Special Features. Five patients of 100 showed subcutaneous nodules. This figure is not far removed from the average incidence of this manifestation for all ages. There was one case of rheumatoid arthritis in which in addition to involvement of the peripheral joints the patient presented the symptoms and x-ray findings of rheumatoid spondylitis. There was one patient in whom so-called psoriatic arthritis developed after the age of sixty. However, the psoriasis itself had appeared a number of years earlier.

Clinical Manifestations. Generally speaking, rheumatoid arthritis in patients over sixty years of age presents a picture which does not differ markedly from that seen in younger age groups. The onset may be sudden or gradual. When the onset is acute, pain and swelling of the joints come on rapidly and may be associated with chills, fever, prostration and other features of an acute illness. In most cases the onset is gradual, symptoms appearing first in only one joint. Often there is pain and stiffness in this particular joint for weeks or even months before other joints are affected. Regardless of whether the symptoms develop suddenly or gradually the disease eventually assumes a chronic course. The characteristic clinical features are pain and swelling of the joints, the migratory character of the joint symptoms, the tendency to symmetrical distribution and the eventual ankylosis and deformity of the joints if the disease is not arrested.

Precipitating Factors. The majority of patients in this series (65 per cent) were not able to name any particular episode or physical disability which they could incriminate as a precipitating factor in the onset of their arthritis. Many of these elderly patients, however, were living alone and we got the impression that not infrequently loneliness and mental depression played an important part in precipitating the joint symptoms. The actual precipitating factors

mentioned by thirty-five patients are listed in Table II.

The two most prevalent precipitating factors in this small group were psychic trauma and upper respiratory infections. In five cases a cardiovascular accident pre-

TABLE II

PRECIPITATING FACTORS

Psychic trauma	11
Upper respiratory infection	11
Exposure	3
Myocardial infarction or coronary disease	5
Physical trauma	5

TABLE III

INCIDENCE OF JOINT INVOLVEMENT

Metacarpophalangeal joint of hand . .	71
Proximal interphalangeal joint of hand	68
Knee	59
Shoulder	55
Wrist	48
Ankle	38
Elbow	34
Feet	17

ceded the onset of symptoms. Interestingly enough, in all five of these cases the shoulders were the first joints to be affected.

Joint Involvement. The frequency of joint involvement is noted in Table III. Twenty-seven patients manifested the disease in the upper extremities only while in only four patients were the lower extremities solely implicated. In the remaining sixty-nine, both upper and lower extremities were involved. The striking feature about the joint involvement was the comparatively large number with implication of one or both shoulders. In rheumatoid arthritis of the younger age groups shoulder involvement is rather infrequent, ranking seventh in large series of cases reported,⁴ whereas in this group it will be noted that the shoulder ranked fourth in frequency of involvement. In the present study the small joints of the hands and fingers were those most frequently involved. In this respect rheumatoid arthritis in the aged is similar to rheumatoid arthritis in the younger age groups. The early involvement of the shoulder and hand in a goodly number of patients was reminiscent of the so-called "shoulder-hand syndrome." However, subsequent involvement of other joints and a high sedimentation rate

indicated the real nature of the ailment. The following case illustrates this point:

CASE REPORT

M. D., a sixty-three year old housewife, complained of pain in shoulders and hand of six months' duration. Onset was abrupt, with no known precipitating factor, and characterized by sharp pain in the right shoulder. Shortly after there was involvement of the left shoulder. The pain radiated down the arms and forearms and was associated with the sensation of "pins and needles." Subsequently the fingers of both hands became stiff, painful and swollen.

Past history was one of good general health except for six attacks of renal colic due to calculi. The last attack of colic was nine years before onset of present illness. The patient had lost 30 pounds since onset of present illness.

Physical examination revealed a senescent female who appeared chronically ill. General physical examination was within normal limits. Blood pressure was 130/90. She was unable to elevate or abduct either arm above shoulder level. The muscles of the shoulder girdle were extremely sensitive to palpation. Rotation of shoulders was painful and limited. Both hands were diffusely swollen, the swelling involving the fingers and dorsum of the hand. She was unable to make a fist with either hand. Her palms were warm and moist. Lower extremities were normal.

Laboratory findings were as follows: urine specific gravity, 1.024; sugar, negative; albumin, trace; one to three red blood cells per high power field; eight to ten white blood cells per high power field; epithelial cells, few; many urates. Blood count revealed hemoglobin 11.5 gm., 80 per cent; red blood cells, 4,100,000; white blood cells, 6,300. The differential count was polymorphonuclears, 62 per cent; lymphocytes, 35 per cent; monocytes, 1 per cent; eosinophiles, 2 per cent; platelets, adequate. Blood uric acid was 2.5 mg. per cent. Sedimentation rate (Westergren method) was 55 mm. in one hour.

X-rays of both shoulders revealed moderate osteoporosis of bones. X-rays of hands and wrists exhibited moderate decalcification and soft tissue thickening of the fingers.

In this patient the diagnosis of a shoulder-hand syndrome was at first entertained but because of the high sedimentation rate and anemia it was finally concluded that the patient had

rheumatoid arthritis. She was given three injections of gold salts (total dosage 60 mg.) after which she discontinued attendance at the clinic. In a follow-up investigation four years later it was found that she gradually improved over a period of months without any special therapy, then relapsed, with involvement not only of upper extremities but also of the knees and ankles.

As might be expected in this age group osteoarthritis was quite frequently found in association with the rheumatoid manifestations. Thus it was not unusual to find a typical case of rheumatoid arthritis affecting the small joints of the hand but associated with an obvious osteoarthritis in the knees or spine. Also, the terminal interphalangeal joints of the fingers might reveal Heberden's nodes while the proximal interphalangeal and metacarpo-phalangeal joints would be the seat of typical rheumatoid arthritis.

There was a very low incidence of hip, back and jaw involvement in this series of cases.

Constitutional Symptoms. A comparatively small percentage of our patients gave a history of loss of weight but many complained of lassitude and easy fatigability. As might be expected in individuals of this age a considerable number had hypertensive vascular disease although the incidence of cardiovascular disease was no higher than in any other unselected group of elderly patients.

Laboratory Findings. The blood count showed remarkably little variation from normal. In 72 per cent of the patients the red blood corpuscles numbered 4,000,000 or more and in 87 per cent the hemoglobin was recorded as 11 gm. or more. A remarkably small percentage of these patients showed an anemia comparable to that frequently encountered in rheumatoid arthritis of young adults.

The white blood corpuscles were under 10,000 per cu. mm. in 64 per cent of the cases. When above 100,000 the excess was small in the great majority of cases.

The sedimentation rate before treatment was elevated in 96.8 per cent of cases.

(Table iv.) Only three patients in the entire series of ninety-four on whom records of sedimentation rates were available showed a normal rate by the Westergren method (i.e., below 20 mm. in one hour).

The agglutination test with the patients' serum against group A hemolytic strepto-

TABLE IV
INITIAL SEDIMENTATION RATE OF RED BLOOD CORPUSCLES

Rate (mm.)	No. of Cases
Below 20.....	3
20-29.....	5
30-39.....	11
40-49.....	36
50 and over.....	39

coccus was made on twenty-nine patients and gave a positive reaction (1 to 180 or higher) in 48 per cent of the cases. This is slightly below the figure usually obtained in rheumatoid patients of all ages.

X-ray studies of the joints were not carried out as a routine on every patient included in this study. In many cases the clinical picture was so characteristic of rheumatoid arthritis that x-rays were not deemed essential. Of forty-two who did have x-ray studies thirty-four or 81 per cent showed findings typical of rheumatoid arthritis. The most common, indeed the almost universal finding, was osteoporosis of the bones adjacent to the affected joints. Many of these patients, of course, showed some osteoarthritic changes as was to be expected in patients of this age.

Treatment. Practically all of the patients included in this study were ambulant cases. Routine treatment included general advice regarding daily rest periods and avoidance of emotional strain, fatigue and exposure to cold. Practically all of the patients received physiotherapy in some form. Streptococcus vaccine was used in a few cases and several others received fever therapy and brief periods of hospitalization. Blood transfusions were given in selected cases. A few of the patients made short sojourns to some dry, hot climate. None of these methods of treatment seemed to produce much permanent benefit although some showed temporary remission or improvement.

Forty-nine patients in the series received adequate treatment with gold salts. The preparations used were aurothioglucose (solganal-B oleosum) or gold sodium thiomalate (myochrysine).^{*} The dosage ordinarily used was as follows: An initial intra-

TABLE V
IMMEDIATE RESULTS OF GOLD THERAPY IN FORTY-NINE PATIENTS WHO RECEIVED ADEQUATE AMOUNTS OF GOLD SALTS

Remission.....	15	} 68%
Major improvement.....	18	
Minor improvement.....	6	
No improvement.....	8	
Uncertain.....	2	
	49	

muscular dose of 10 mg. was followed at weekly intervals by two or three injections of 25 mg. each. Subsequently, doses of 50 mg. were given weekly with a few patients receiving 100 mg. weekly. Table v summarizes the immediate results of gold therapy in forty-nine patients who received what is rather arbitrarily considered to be an adequate total dosage of gold salts, i.e., 500 mg. or more. The total dosage administered ranged from this minimum to a maximum of 5,360 mg., with the majority receiving between 1,000 and 1,500 mg. The therapeutic criteria for response were those recommended by the American Rheumatism Association.² The small group who received less than 500 mg. of gold salts were classified with the controls.

It will be noted that in this comparatively small series of forty-nine cases 68 per cent had a remission or showed major improvement. The results in the remaining 30 per cent were indifferent.

These immediate results compare favorably with those obtained by other investigators and also with our own results in a previous study of gold treatment in 245 unselected cases of rheumatoid arthritis.³

Table vi indicates the results of treatment in a group of fifty-one patients who received no gold (or an inadequate amount of gold) and who had to depend on other forms of

treatment such as physiotherapy. In this group who received no gold or an inadequate amount of gold only eleven or 29 per cent had remission or showed major improvement. This is in sharp contrast to the thirty-one cases (68 per cent) who had

TABLE VI
RESULTS OF TREATMENT IN FIFTY-ONE NON-GOLD TREATED CASES AND THOSE RECEIVING INADEQUATE AMOUNTS OF GOLD

Remission.....	2	} 29%
Major improvement.....	9	
Minor improvement.....	6	
No improvement.....	21	
Uncertain.....	13	
	51	

remission or major improvement under gold therapy.

Relapses. We have been able to follow forty-eight patients in this series for a period of one to ten years. (Table vii.) Of these, thirty-two have been followed one to five years, sixteen for five to ten years. Of these forty-eight twenty-eight had been treated with gold salts while twenty had received no gold or an inadequate amount. Of the twenty-eight patients in this group treated

TABLE VII
DURATION OF OBSERVATION

Duration (yr.)	Patients Treated with Gold Salts	Patients Treated without Gold Salts or an Inadequate Amount
Less than 1.....	21	31
1-5.....	20	12
5-10.....	8	8
Total.....	49	51

with gold salts fifteen (53 per cent) had attained an immediate remission or major improvement. Over this period of observation five of these fifteen relapsed and two of the five again sustained major improvement or remission with further gold treatment.

In the group of twenty who had received no gold salts or an inadequate amount and who were followed for a period of one to ten years there were seven (35 per cent) who

* We are greatly indebted to the Schering Corporation for supplying the solganal-B for this study and to Merck & Co., Inc. for the myochrysine.

had attained either major improvement or remission. Of these seven there were two who had relapsed with no subsequent improvement.

It is interesting but profitless to speculate as to how many patients in each group would have relapsed had it been possible to follow them all for a period of five or ten years. Naturally, in this age group death often precludes a long follow-up period. Thus there were nine known deaths in the entire group in the first five years of observation.

Toxic Reactions. Of the forty-nine patients who received gold therapy twelve showed toxic reactions. In eleven cases this took the form of a squamous dermatitis. In one case the dermatitis was combined with a stomatitis. In only one case was the dermatitis severe enough to be classified as exfoliative. All of these patients were relieved of their rash after gold was discontinued although in several instances its disappearance was very gradual.

Deaths. There were fourteen deaths in this group of patients during the period in which they were followed. In five patients the cause of death was uncertain or unknown. In five the cause of death was carcinoma and in the remaining four death was due to myocardial infarction. It is always a cause for speculation when the physician sees an elderly patient with rheumatoid arthritis, particularly one with a very high sedimentation rate, as to whether or not some other underlying systemic disease such as carcinoma may be present. Unusually careful search should be made in these individuals to uncover a possible neoplasm.

COMMENTS

A survey of the findings in this study of 100 cases of patients with rheumatoid arthritis in the aged would indicate that the disease in old people does not differ essentially from that seen in the earlier decades. There are a few points, however, that are worth emphasis. It is interesting that in this particular series sex incidence was exactly

the same. There were fifty males and fifty females. One is tempted to say that the male becomes more susceptible to rheumatoid arthritis in old age. However, it would be necessary to study a much larger series of cases before this could be put down as an actual fact.

In spite of statements which have been made that rheumatoid arthritis in the aged runs a milder course than it does in younger individuals we can find no evidence to support this in our present study. Rheumatoid arthritis can be mild or severe, indolent or rapidly progressive at all ages. This is true even in children who have so-called Still's disease, a condition which can be very mild or extremely severe and crippling. The same is true of the present series. Some of our elderly patients escaped with very mild attacks; others ran a severe and almost totally crippling course.

So far as joint involvement is concerned we were particularly intrigued by the incidence of shoulder involvement in this series of cases and the frequency with which the onset of the disease was first noted in the shoulder. In a considerable number the condition was ushered in by what seemed to be an almost typical shoulder-hand syndrome and certainly would have been diagnosed as such had it not progressed to the involvement of other joints. This suggests that the shoulder-hand syndrome may be more closely related to rheumatoid arthritis than has been supposed in the past.

The laboratory findings have not differed in any essential respect from those seen in the earlier decades, with the possible exception that secondary anemia is less frequently encountered and a very high sedimentation rate is a frequent finding. X-rays usually showed osteoporosis but often, because of the age of the patient, the picture was complicated by the presence of more or less osteo-arthritis.

So far as treatment is concerned there is nothing much that can be said except that elderly patients tolerate gold therapy very well and certainly have no more tendency to toxic reactions than younger patients.

The results with gold therapy were quite satisfactory. There was, of course, the usual tendency to relapse.

SUMMARY AND CONCLUSIONS

1. Rheumatoid arthritis in the aged does not differ in any essential respect from rheumatoid arthritis in the earlier decades of life.

2. In this study there was a higher incidence of the disease in males than that observed in younger patients. There was a low incidence of secondary anemia and not infrequently a very rapid sedimentation rate.

3. One or both shoulders were frequently involved and in a few cases the disease started in the shoulder joint. In some in-

stances the picture was quite suggestive of the so-called shoulder-hand syndrome.

4. Elderly, rheumatoid patients tolerate gold therapy just as well, perhaps even better, than younger patients and the results are equally as good. There is, however, the usual tendency to relapse.

REFERENCES

1. SCHNELL, A. The clinical features of rheumatic infection in the old. *Acta med. Scandinav.*, 106: 345-351, 1941.
2. STEINBROCKER, OTTO, TRAEGER, C. H. and BATTERMAN, R. C. Therapeutic criteria in rheumatoid arthritis. *J. A. M. A.*, 140: 659-662, 1949.
3. CECIL, R. L., KAMMERER, W. H. and DEPRUME, F. J. Gold salts in the treatment of rheumatoid arthritis: a study of 245 cases. *Ann. Int. Med.*, 16: 811-827, 1942.
4. COMROE, B. I. *Arthritis and Allied Conditions*, 4th ed. Philadelphia, 1949. Lea & Febiger.

The L.E. (Lupus Erythematosus) Cell*

Clinical and Chemical Studies

STANLEY L. LEE, M.D., SIDNEY R. MICHAEL, M.D. and I. LUTFI VURAL, M.D.

New York, New York

IN 1948 Hargraves, Richmond and Morton¹ first reported the finding of a peculiar cell, which they called the L.E. cell, in the bone marrow of cases of disseminated lupus erythematosus. Subsequently Haserick and Sundberg² confirmed their findings and indicated the specificity of this element for the disease. Further reports by Sundberg and Lick,³ Haserick and Bortz,⁴ and Hargraves⁵ made the following points: (1) The L.E. cell may be defined as a polymorphonuclear leukocyte containing a large round homogeneous inclusion body which is stained by basic dyes and is Feulgen-positive.² It resembles but is to be differentiated from what Hargraves called the tart cell in which the inclusion body can readily be recognized as a cell nucleus. (2) The L.E. cell can be demonstrated in bone marrow and peripheral blood of most patients with acute disseminated lupus erythematosus in relapse.¹⁻³ (3) It has not been proved to occur in any other disease. (4) The cell can only be found when bone marrow or blood is collected with an anticoagulant (heparin, oxalate or citrate).³⁻⁵ (5) Identical cells can be produced in normal bone marrow by the addition to it of plasma from a case of acute disseminated lupus erythematosus.^{4,5}

Recent studies of postmortem material by Klemperer et al.⁶ have established a new anatomic diagnostic criterion in disseminated lupus, namely, the finding of a peculiar nuclear alteration in mesenchymal cells. This change consists of homogenization and swelling of the nucleus, with complete loss of chromatin network and the

formation, in certain loci and certain cases, of huge masses of altered nuclear material. Histochemical studies of these lesions have showed the material to contain large quantities of desoxyribose nucleic acid in a depolymerized state.

The smallest of the hematoxylin-staining bodies described by Klemperer and his associates bear a striking resemblance to the Hargraves L.E. cell. It appeared to us that if both these findings were indeed specific for and universal in disseminated lupus erythematosus, they probably were related; and that information concerning the production of these unusual cytologic alterations might shed some light on the pathologic physiology of the disease. The objectives in this study were, then, to confirm the specificity of the L.E. cell and to establish its relationship, if any, to the hematoxylin-staining bodies by determining the chemical constitution of the L.E. cell and the mechanism of its formation.

MATERIAL AND METHODS

Seventeen patients in whom the diagnosis of acute disseminated lupus erythematosus was made were admitted to the wards of the Mount Sinai Hospital during the period of this study. All these were examined; in addition, cases of rheumatic fever, rheumatoid arthritis, periarteritis nodosa, dermatomyositis, scleroderma, subacute bacterial endocarditis, carcinomatosis and various hematologic disorders were used as control material.

For routine⁷ diagnostic examinations of peripheral blood⁸ or bone marrow the following techniques¹² were used: Five milliliters of blood collected in a test tube containing 1 mg. of dried

* From the First Medical Service and the Laboratories of The Mount Sinai Hospital, New York, N. Y. The photometric studies herein described were carried out with the aid of a grant from the Daisy Levey Foundation.

heparin were allowed to stand until there was a clear demarcation between red cells and plasma. The latter (buffy coat) was removed with a pipette and transferred to a water bath (37°C.) for fifteen to thirty minutes. It was then centrifuged and the supernatant plasma was poured off. The sediment, consisting chiefly of leukocytes, platelets and a few red cells, was resuspended in the remaining plasma droplet, spread on a glass slide in the usual way and stained by the Jenner-Giemsa method. Bone marrow was handled in the same manner except that 1 ml. of marrow and 0.2 mg. of heparin were used. (Fig. 1.)

Alternatively, equal volumes of cell-free L.E. plasma and heparinized normal marrow buffy coat or normal or leukemic peripheral blood buffy coat were mixed and incubated as before. Titrations of the potency of given plasma were carried out by determining the greatest dilution of plasma which produced L.E. cells in a given quantity of substrate cells. Comparisons between different plasmas or fractions of the same plasma were also made by determining the number of L.E. cells induced per 1,000 granulocytes.

Serial preparations were made by adding the same quantity of substrate cells to each of several small tubes. These were centrifuged and the plasma poured off. Then without resuspending the "button" a potent L.E. plasma was added to each succeeding tube at one-minute intervals.

Plasma protein fractionation was carried out by a modification of Svensson's⁷ procedure. All dialysis was performed in a refrigerator. The plasma was placed in dialyzing bags, ammonium sulfate solution was dialyzed in. The precipitate was spun down, washed in solution of the same strength; it was then resuspended in a small quantity of normal saline. The following ammonium sulfate fractions were prepared: 33 per cent, 40 per cent, 55 per cent and 100 per cent saturated.

Portions of the L.E. plasma and the fractions were stored at -4°C., at +4°C. and at room temperature. Other parts were subjected to repeated freezing and thawing.

RESULTS

Clinical. The L.E. cell was found in the peripheral blood and bone marrow in every proved case of acute disseminated lupus erythematosus examined. It was not found in the marrow of any case which did not

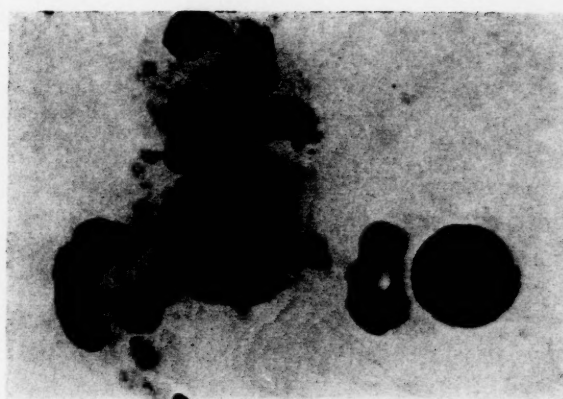


FIG. 1. Typical L.E. cell in buffy coat preparation. Jenner-Giemsa $\times 960$.

exhibit it in the peripheral blood. However, it was usually present in greater numbers in the marrow. In a few cases a larger number of L.E. cells were formed from normal blood or marrow cells than from the patient's own leukocytes. In all cases it was possible to induce the phenomenon in normal white blood cell concentrates. It appears that the demonstration of L.E. cells is possible in most if not all cases of disseminated lupus erythematosus and that the peripheral blood is satisfactory for the test. In our experience up to this time remission, whether spontaneous or induced (cortisone), did not cause the disappearance of the phenomenon.

The L.E. cell was not demonstrated by us in any condition except lupus erythematosus. However, two cases in which L.E. cells were found in both peripheral blood and bone marrow exhibited certain unusual clinical and laboratory features in addition to the usual symptoms and signs, and the diagnosis in these cases is still in doubt.

Of particular interest was the uniform failure to demonstrate these cells in any other of the diseases involving vascular or connective tissues. Cases of diffuse vascular disease, rheumatoid arthritis, dermatomyositis, scleroderma, rheumatic heart disease (active and inactive) and subacute bacterial endocarditis were examined with negative results. Tart cells and erythrophagocytosis were seen in these as well as in other conditions. L.E. cells were not seen in any patient

having a blood dyscrasia, lymphoma or carcinoma.

In a case of primary amyloidosis involving (among other loci) the bone marrow, a cell identical by Jenner-Giemsa stain with the L.E. cell was seen in a smear of heparinized marrow. In a search of many slides only this single cell was found; all the slides, however, showed large masses of homogeneous material which took the usual stains for amyloid and which did not stain with the Feulgen or methyl green methods. Since this material (undoubtedly amyloid) was present in large quantity and since it seemed identical by Jenner-Giemsa stain with the intracellular material of the single L.E. cell, we feel justified in the assumption that that material also was amyloid.* This has been the only case which we have observed in which an L.E. cell was found and in which the diagnosis was definitely not acute disseminated lupus erythematosus. Hargraves is reported¹³ to have found L.E. cells in a case of multiple myeloma; amyloidosis of the bone marrow occurs in that disease and it is possible that his case may have been similar to this of ours.

Experimental. Previous reports indicated that the factor responsible for the L.E. cell phenomenon was a plasma constituent. We found that on dialyzing plasma against normal saline solution no activity passed into the saline. Therefore, it seemed likely that the factor was a protein or was intimately bound to protein. Preliminary separation indicated it to be a globulin. Using a modification of Svensson's⁷ method we found that the activity of the various fractions paralleled the expected concentration of gamma globulin. Due to technical difficulties we were unable to confirm this fact with electrophoretic patterns or separations. Haserick⁸ has demonstrated by such means the presence of the active factor in the gamma globulin fraction.

The activity of whole plasma was always

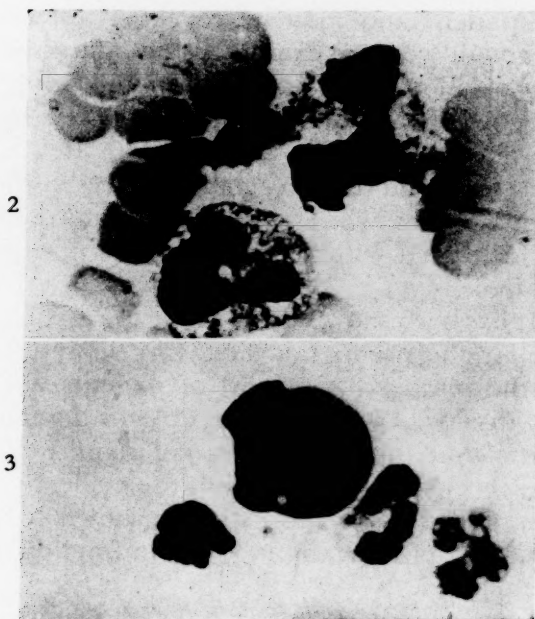
greater than that of the most concentrated fraction which we were able to prepare. There was great variability in the titratable activity of the plasma of different patients, a range from $\frac{1}{10}$ to $\frac{1}{640}$ being encountered. This could not be correlated with the clinical activity of the disease. Activity did not depend on the presence of complement and was unaltered by freezing or thawing of the plasma, by passage through a Seitz filter or by exposure to ammonium sulfate. Potency was retained after several months at deep freeze temperatures, several weeks at icebox temperature, but only a few days at room temperature. This last result was possibly the result of bacterial contamination.

Previous authors have emphasized the failure to find L.E. cells in smears made directly from marrow or blood. It has been supposed that the presence of an anticoagulant in some way potentiates the activity of the plasma factor. Hargraves⁵ has shown that all anticoagulants are equally useful in this respect. We have been able consistently to demonstrate L.E. cells in clotted blood from patients with the disease although we, too, have never seen them in smears made from freshly drawn blood or marrow.

As a result of this finding it seemed that the one element necessary for activation of the plasma fraction was time. This was then studied by incubation of a known active plasma with normal white cells for varying periods of time. Smears were made at one-minute intervals for the first five minutes. L.E. cells were first found after two minutes of incubation and in all smears made thereafter, reaching their greatest concentration after twenty to thirty minutes.

This method was utilized also for the study of the early cytologic changes leading to the formation of L.E. cells. Alterations which seemed significant were first seen in scattered polymorphonuclear leukocytes after two minutes of incubation, although the exact time varied with different preparations. These changes involved the cell nuclei. One lobe of a nucleus, or the entire nucleus, would undergo homogenization, swelling and assume the reddish purple color

* Subsequently, this slide was decolorized and stained by the Feulgen method. The inclusion body of the single L.E. cell was Feulgen-negative; it was, then, chemically different from a true L.E. inclusion body.



FIGS. 2 and 3. Early nuclear alterations in polynuclear leukocytes leading to formation of L.E. bodies. Buffy coat preparations, two-minute incubation. Jenner-Giemsa $\times 960$.

characteristic of the L.E. cell inclusion. In the two-minute preparation these cells were still identifiable, their cytoplasm was more or less intact. In this and in later preparations free homogeneous masses identical in appearance to these altered nuclei were seen. An occasional cell with altered nucleus was surrounded by a circle of intact leukocytes (what Haserick⁴ has described as a rosette). (Figs. 2 to 4.)

Other information concerning the mechanism of formation of the L.E. cell was obtained by the use of abnormal white cells as substrate material. Active plasma was incubated with white cells from cases of chronic myelocytic leukemia and chronic lymphatic leukemia, and from a patient having a monocytosis of 25 to 30 per cent. The myeloid white cells responded to the stimulus of the L.E. plasma by a most striking phagocytosis of erythrocytes. L.E. cells were found but they were scarce. Cells as immature as neutrophilic myelocytes could be identified as phagocytes. When lymphocytes (in practically pure culture) from a case of lymphatic leukemia were subjected to the same stimulus, no effect at all was

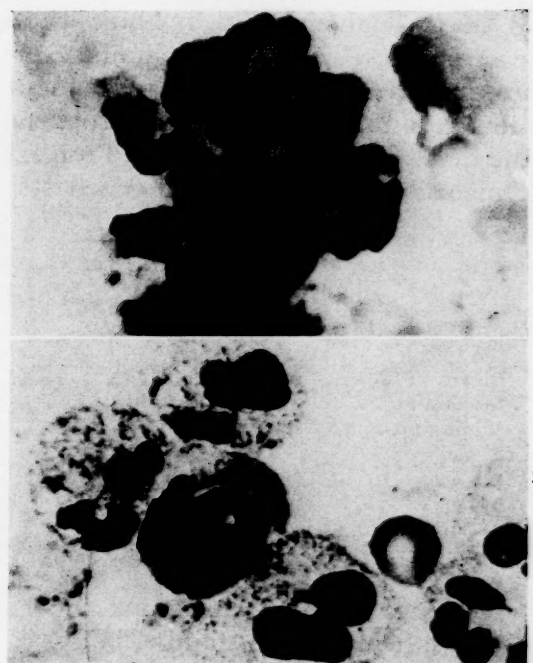


FIG. 4. Rosette formation in which the surrounded masses can be identified as altered cells. Buffy coat preparation. Jenner-Giemsa $\times 960$.

FIG. 5. Phagocytosis of intact lymphocyte by polynuclear leukocyte (tart cell). Mixed myeloid and lymphatic leukemia buffy coat and L.E. plasma. Jenner-Giemsa $\times 960$.

noted. Then mixtures of myeloid and lymphatic white cells were treated with L.E. plasma. L.E. cells were found in large numbers; even more striking was phagocytosis of intact lymphocytes, again by mature and immature granulocytes. It was possible in this preparation to make out all gradations of the included body from unaltered lymphocyte to homogeneous L.E. body. When leukocytes of which a high percentage were monocytes were used as substrate, L.E. cells were produced in which the including cell was a monocyte. (Fig. 5.)

L.E. cells were studied cytochemically by means of Feulgen and methyl green^{9,10} stains. The inclusion body was found to stain with both these methods, establishing its content of desoxyribose nucleic acid. Feulgen-methyl green ratios were then obtained for a series of L.E. cells according to the method of Leuchtenberger^{9,11} and as reported by Klemperer *et al.*⁶ each cell being measured first with methyl green and

then after Feulgen stain.* These ratios, when compared with values obtained for a series of normal lymphocytes (Table 1), demonstrate that a considerable proportion of the desoxyribose nucleic acid in the L.E. cell inclusion is in a depolymerized state.

TABLE 1
Optical Density (Feulgen)
Optical Density (Methyl Green)

A. Normal Cells (Lymphocytes) (15 Cells)	
Mean.....	0.83
Maximum.....	0.92
Minimum.....	0.77
B. L.E. Cells (25 Cells)	
Mean.....	2.18
Maximum.....	7.0
Minimum.....	0.80

The findings thus definitely link the L.E. cell to the hematoxylin-staining body.

COMMENTS AND CONCLUSIONS

Previous reports have stressed the diagnostic importance of the L.E. cell in acute disseminated lupus erythematosus. Our findings serve to underline this point. The test for L.E. cells is both a sensitive and a specific one; it involves little discomfort to

* Smears are made of the material to be studied; these are fixed immediately in Carnoy's acetic alcohol and stained for twenty-four hours in a 0.5 per cent aqueous solution of especially purified (by repeated extractions with chloroform) methyl green (National Aniline Company, C.I. No. 685). The slide is decolorized in tertiary butyl alcohol for one hour at 55°C. and then is searched for L.E. cells. Appropriate cells are marked (preferably with a Leitz Objektmarkierer) and their immediate neighborhood on the slide mapped so that individual L.E. cells may be found and identified again.

Measurements of light transmission of individual previously marked L.E. bodies are made by means of a microphotometer built for our laboratory by Dr. Boris Gueft and patterned after the one in use at the Zoology Laboratories of Columbia University. For these measurements a zirconium arc light source and a Wratten No. 26 filter are employed.

Upon completion of the measurements, the same slide is restained by the Feulgen method. The same L.E. bodies are measured again, this time using a Farrand interference filter having an absorption maximum at 570 μ .

Optical densities are calculated from the observed transmission values. Ratios of optical densities are calculated for individual cells. In the case of normal cells these ratios are remarkably constant, but for L.E. cells a strikingly wide variability exists.

the patient and may be repeated at will. Although we have examined the bone marrow of all patients included in this study, we now rely on peripheral blood alone for the demonstration of the L.E. cell. If L.E. cells are found only in small numbers in the patient's own white cells, the plasma may be incubated with a concentrate of normal white cells.

It has been shown that the factor responsible for the production of L.E. cells resides in the plasma (or serum) of patients with the disease. We have been able to demonstrate that this factor does not require the presence of an anticoagulant to be effective. Haserick and we have further shown it to be a part of the gamma globulin fraction of the plasma.

Our cytologic studies have shown that the inclusion body of the L.E. cell is the result of a peculiar and unique form of nuclear degeneration affecting polymorphonuclear leukocytes and probably lymphocytes. Its position inside a leukocyte is probably, in most cases, the result of phagocytosis since we have found that the L.E. cell-inducing factor produces a very powerful stimulus to phagocytosis.

Finally, by means of cytochemical analysis, we have confirmed the nuclear origin of the inclusion bodies and have found them to be identical with the hematoxylin-staining bodies described by Klempner et al., i.e., to contain a large proportion of depolymerized desoxyribose nucleic acid. It is this depolymerization of the chromatin material, presumably, which leads to the homogenization and swelling so characteristic of both the L.E. cell and the hematoxylin-staining body.

It would, therefore, appear that in the gamma globulin fraction of plasma of patients with acute disseminated lupus erythematosus there is a factor capable of altering the metabolism of desoxyribose nucleic acid. This factor is responsible for the production of L.E. cells and probably of hematoxylin-staining bodies; whether it can be related to other manifestations of the disease remains to be seen.

SUMMARY

1. Seventeen cases of acute disseminated lupus erythematosus have been studied with regard to L.E. cells; such cells have been found in all cases, in both marrow and peripheral blood.*

2. In a large body of control material only one definite false positive has been found. This was a case of amyloidosis of the bone marrow. The L.E. cell seen was shown to be chemically different from the true L.E. cell.

3. Biochemical studies have revealed the following facts: The L.E. cell can be found in clotted blood; it does not depend on the presence of an anticoagulant but only on time outside the body for its formation. The included body of the L.E. cell is altered nuclear material derived from polymorphonuclear leukocytes and lymphocytes. This

* Since the submission of this material for publication, Berman et al. (*Am. J. Clin. Path.*, 20: 403-418, 1950) have reported the finding of L.E. cells in bone marrows of a patient with pernicious anemia and a case of dermatitis herpetiformis. N. B. Kurnick (personal communication) has seen them in a patient who was found at autopsy to have miliary tuberculosis. Our own experience has been broadened by the addition of six more patients exhibiting the phenomenon. Of these, five have been shown, clinically or histologically, to have acute disseminated erythematous lupus. In addition, one of the patients described in the cases referred to in the body of this paper as doubtful has been proved to be suffering from this disease; unfortunately, we have lost track of the other. Our sixth recent case was a man of forty-seven with a severe acute hemolytic anemia to which he eventually succumbed. His spleen, removed at operation, showed no evidence of lupus, and except for the L.E. cells, there was nothing in the clinical picture to suggest the diagnosis.

In the absence of a postmortem examination we have classified this case as false positive. Finally, we have recently seen one definitely proved case of a patient with acute disseminated lupus in whom repeated examinations have failed to show L.E. cells. Our experience to date then shows the phenomenon to have sensitivity and specificity both of about 96 per cent.

material contains partially depolymerized desoxyribose nucleic acid and is identical both optically and chemically with the hematoxylin-staining body.

REFERENCES

1. HARGRAVES, M. M., RICHMOND, H. and MORTON, R. Presentation of two bone marrow elements: the "tart" cell and the "L.E. cell." *Proc. Staff Meet., Mayo Clin.*, 23: 25, 1948.
2. HASERICK, J. R. and SUNDBERG, R. D. The bone marrow as a diagnostic aid in acute disseminated lupus erythematosus. *J. Invest. Dermat.*, 11: 209, 1948.
3. SUNDBERG, R. D. and LICK, N. "L.E." cells in blood in acute disseminated lupus erythematosus. *J. Invest. Dermat.*, 13: 47, 1949.
4. HASERICK, J. R. and BORTZ, D. W. Normal bone marrow inclusion phenomena induced by lupus erythematosus plasma. *J. Invest. Dermat.*, 12: 83, 1949.
5. HARGRAVES, M. M. Production *in vitro* of the L.E. cell phenomenon: use of normal bone marrow elements and blood plasma from patients with acute disseminated lupus erythematosus. *Proc. Staff Meet., Mayo Clin.*, 24: 234, 1949.
6. KLEMPERER, P., GUEFT, B., LEE, S. L., LEUCHTENBERGER, C. and POLLISTER, A. W. Cytologic changes in disseminated lupus erythematosus. *Arch. Path.*, in press.
7. SVENSSON, H. Fractionation of serum with ammonium sulfate and water dialysis studied with electrophoresis. *J. Biol. Chem.*, 139: 805, 1941.
8. HASERICK, J. R., LEWIS, L. A. and BORTZ, D. W. Blood factor in acute disseminated lupus erythematosus. I. Determination of gamma globulin as specific plasma fraction. *Am. J. M. Sc.*, 219: 660, 1950.
9. POLLISTER, A. W. and RIS, H. R. Nucleoprotein determination in cytological preparations. *Cold Spring Harbor Symp., Quant. Biol.*, 12: 147-157, 1947.
10. POLLISTER, A. W. and LEUCHTENBERGER, C. The nature of the specificity of methyl green for chromatin. *Proc. Nat. Acad. Sc.*, 2: 111-116, 1949.
11. POLLISTER, A. W. and MOSES, M. J. A. A simplified apparatus for photometric analysis and photomicrography. *J. Gen. Physiol.*, 32: 567, 1949.
12. ROSENTHAL, N. Personal communication.
13. MONTGOMERY, H. and MACCREIGHT, W. G. Disseminated lupus erythematosus. *Arch. Dermat. & Syph.*, 60: 356, 1949.

Treatment of Leukemia with Aminopterin*

LEO M. MEYER, M.D. and ABBOTT NEWMAN, M.D.

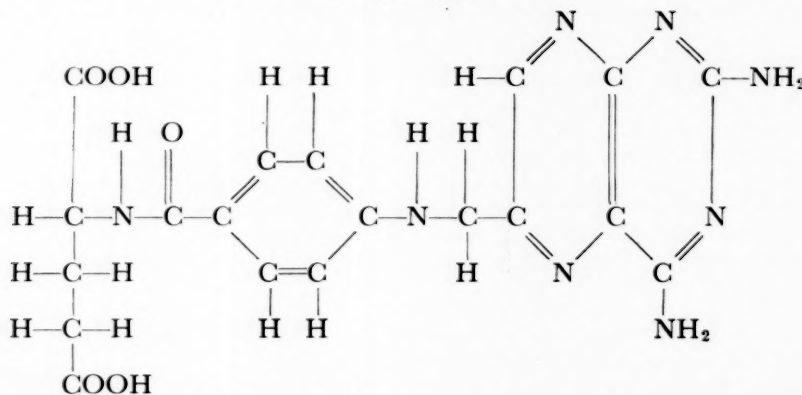
Brooklyn, New York

CLINICAL trials with potent biologic antagonists of pteroyl glutamic acid (folic acid) in the treatment of leukemia followed soon after the discovery that folic acid-deficient diets produced changes in tumor growth and blood-forming organs. Recently, attention has been focused on the amino derivatives of pteroyl glutamic acid in which the 4-hydroxyl group is replaced by the NH_2 radical.¹

but cures were not demonstrated. Weir, Welch and Heinle have extended studies of folic acid antagonists on mouse leukemia.¹⁰

The clinical use of antifolic compounds has been most extensively reported in human leukemia. Meyer found temporary improvement with clinical and hematologic response in some patients with acute leukemia treated with pteroyl aspartic acid, methyl pterioic acid and 4-amino pteroyl glutamic acid.^{11,12}

AMINOPTERIN



Studies of folic acid-deficient states on the growth of neoplastic tissue by Little et al.,^{2,3} in which tumor growth was inhibited in chicken sarcoma, led to experiments with the 4-amino-conjugate (aminopterin) demonstrating its inhibiting effect on mouse tumors and occasional cure of rat sarcoma.⁴⁻⁶ Hematologic lesions with changes in the bone marrow and mucosa of the intestinal tract such as are seen in severe folic acid deficiency were noted in mammals given the drug. Mice, rats, guinea pigs and dogs showed a reduction of hematopoietic elements with destruction of bone marrow.^{7,8} Mice with transplanted leukemia were treated with aminopterin by Burchenal and co-workers.⁹ Survival times were prolonged

Farber reported experiences with aminopterin in sixteen children with acute leukemia, describing temporary remissions or improvement in ten cases.¹³ Additional studies on sixty children with acute leukemia treated with several of the antifols indicated clinical or hematologic response in 50 per cent although toxic manifestations due to the drugs administered were common.¹⁴ In a series of forty-three patients with acute leukemia treated with aminopterin Meyer et al. reported hematologic improvement in four and toxic manifestations in twenty-four.¹⁵ Low incidences of remissions in children with acute leukemia were reported by other observers.¹⁶⁻¹⁸ Thiersch and Philips, reviewing the literature,⁷ have found 250

* From the New York Hospital and the Department of Medicine, Cornell University Medical College, New York, N. Y.

cases of acute leukemia in man treated with the antifolic acids, with temporary remissions in thirty per cent. In chronic leukemia, hematologic changes were noted but no effect comparable to that obtained in the cases of acute leukemia occurred.^{15,18,19} In

moderately enlarged. The liver was barely palpable; the spleen could not be felt. Skin and axillary node biopsies revealed infiltration with abnormal lymphocytic cells. Hematologic studies and therapy are shown in Figure 1. A diagnosis of subacute lymphoblastic leukemia was made.

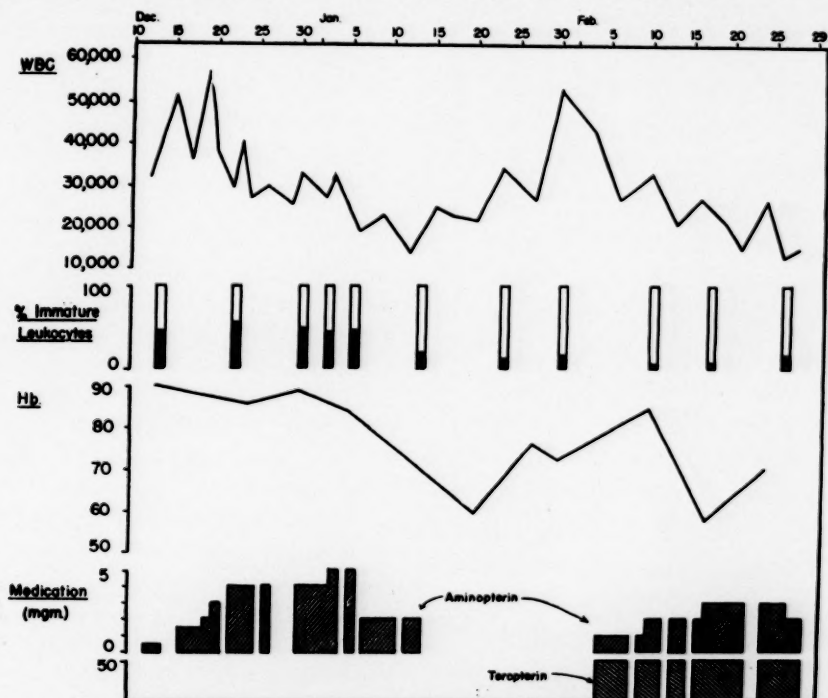


FIG. 1. Patient with subacute lymphocytic leukemia who showed a reduction of lymphocytes and blast cells in the peripheral blood following aminopterin therapy. (Bone marrow was unchanged.) Severe stomatitis developed and was not affected by simultaneous administration of teropterin during a second course.

other human malignant tumors antifolic acid therapy has been disappointing.^{14,20}

The following report is concerned with the treatment with aminopterin* of four patients with acute or subacute leukemia† and one with lymphosarcoma:

CASE REPORTS

CASE I. J. K., a white male sixty-five years of age, was admitted to the New York Hospital on November 20, 1947, because of a dry, red scaly itching of the skin of six months' duration. The patient was a known diabetic for twenty-three years and easily controlled. Physical examination disclosed marked scaly erythema of the skin of the entire body. The nodes were all

* Supplied by Lederle Laboratories Division, American Cyanamid Co., Pearl River, N. Y.

† These cases were included in a summary report of forty-three patients with leukemia treated with aminopterin.¹⁵

The patient received intramuscular aminopterin therapy beginning on December 12, 1947. The dose ranged up to 5 mg. a day. There was a fall in the total number of leukocytes from 41,000 to 20,000/cu. mm. (lymphoblasts 53 to 49 per cent and prolymphocytes 41 to 12 per cent) in one month. Medication was discontinued because of severe stomatitis involving the buccal mucosa of the lips, cheeks and pharynx. These lesions did not respond to penicillin, gentian violet and alkaline mouth washes as long as aminopterin was continued. Twelve days after the drug was discontinued the oral lesions had almost entirely regressed and the leukocytes rose and reached pretreatment levels in sixteen days. During the period of therapy the skin appeared less red but no alteration in size of the lymph nodes took place. The patient was again started on aminopterin intramuscularly, combined with 50 mg. of teropterin, on February 4, 1948. The dose of aminopterin was never higher

than 3 mg./day. After eighteen days of treatment a decline of leukocytes to 14,000/cu. mm. was observed, with immature cells unchanged in number. However, the recurrence of the oral lesions necessitated discontinuing medication. There was no change in the size of the nodes and

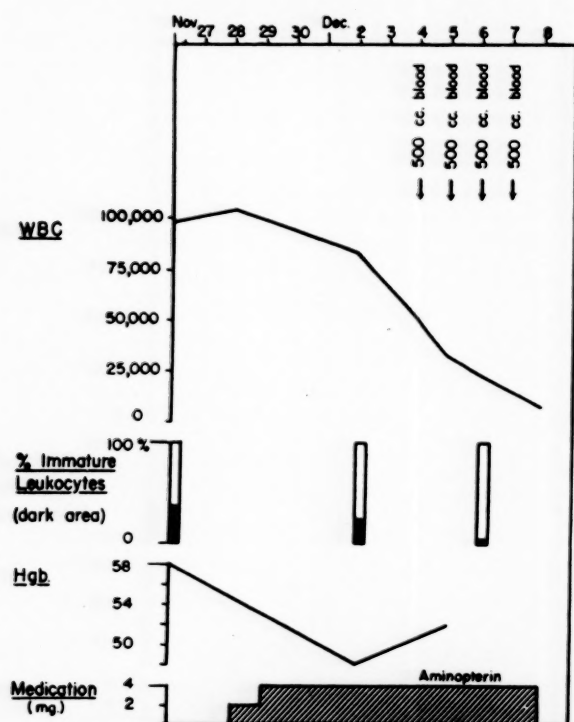


FIG. 2. Patient with subacute myeloid leukemia who showed a reduction of leukocytes and blast cells in peripheral blood following aminopterin therapy. Bone marrow was less cellular after treatment but definitely blastic. Bloody diarrhea and purpura developed during course of therapy.

the liver appeared to have become slightly larger. The skin was as red and scaly as it had been before the first course of treatment. Bone marrow studies made during the first course of aminopterin therapy showed a slight decrease in the total cellularity, with little reduction in the number of immature forms. The hemoglobin and erythrocytes showed a tendency to fall slightly during both periods of treatment and platelets were always low. Megakaryocytes were not observed in the bone marrow. The patient was subsequently treated with progynin, stilbesterol, mercury and tartar emetic without any evidence of improvement. He died on June 3, 1948.

At autopsy enlarged axillary and inguinal nodes composed of packed, homogeneous blast cells were found. The spleen was enlarged, hem-

orrhagic and infiltrated with lymphoblasts. Sections of skin showed dense infiltration with blast cells. Rib and vertebral marrow was markedly hyperplastic with a few scattered areas of fibrosis. (This patient died three months after the last dose of aminopterin was given; therefore, autopsy findings cannot be considered as reflecting the effect of the drug on the hematopoietic tissues.)

CASE II. K. A., a white male aged fifty-nine, was admitted to the New York Hospital on October 23, 1947, because of nausea, anorexia, vomiting and 10-pound weight loss of nine weeks' duration. Prior to this period he suffered a severe infection of a foot which followed a pin-prick. He was treated intensively for one week with penicillin. More recently he noted increasing pallor, weakness and dizzy spells. Physical examination revealed a small nodule (3 cm. in diameter) in the left abdominal wall; liver edge 2 cm. below the right costal border; spleen 1 cm. below the left costal border. No lymphadenopathy was noted. Peripheral blood and bone marrow studies suggested a diagnosis of subacute myeloid leukemia. (Fig. 2.) The patient received ten transfusions of 500 cc. of blood each and 0.5 mg. of urethane three times a day. This latter therapy was discontinued after thirteen days. Four days later aminopterin therapy was begun, namely, 2 mg./day for one day and 4 mg./day for three days. This was followed by a fall in the total leukocytes from 99,000 to 8,100/cu. mm. and a reduction in immature forms from 37 to 24 per cent. The bone marrow also reflected a reduction from marked hyperplasia to a normal total number, but blast forms persisted (23.5 per cent). The hemoglobin and red blood cells fell but this may have been due to the severe bloody diarrhea which developed on the fourth day of aminopterin treatment. Petechiae of the skin and ecchymoses appeared at this time. Platelets were reduced throughout the entire hospital course. Transfusions of blood were administered but the patient expired on the tenth day after the inception of treatment. There was no alteration in the size of the liver, spleen or nodes. Autopsy was not performed.

CASE III. M. S., a white male aged fifty-one, was admitted to the New York Hospital on February 2, 1948, with a six-week history of chest and back pain, weakness, malaise and fever. Laryngitis and furunculosis developed prior to admission. Two weeks before admission

laryngitis developed for which the patient received a sulfonamide drug. One week earlier he had been working with a volatile rubberized cement paint. Physical examination revealed generalized lymphadenopathy and an enlarged liver and spleen.

The initial white blood cell count of the peripheral blood was 61,000/cu. mm., of which 71 per cent were myeloblasts and promyelocytes. The red blood cell count was 2.8 million and hemoglobin 7.5 gm. Sternal bone marrow yielded a total nucleated cell count of 448,000/cu. mm., of which 50 per cent were myeloblasts and 45 per cent promyelocytes. The patient received three transfusions of whole blood on February 13th, 14th and 16th, which raised the red blood cell count to 3.0 million and hemoglobin to 9.5 gm. On February 18, 1948, the total peripheral white count was 29,000/cu. mm. with 78 per cent blasts. Aminopterin, 2.0 mg. daily by intramuscular injection, was given daily for three days for a total of 6.0 mg. A progressive fall in the total white blood cell count of the peripheral blood occurred (with a low of 2,500/cu. mm.) on the third day following the last dose of aminopterin. Blast forms decreased from 75 to 28 per cent and small lymphocytes rose from 11 to 71 per cent. Folic acid in 150 mg. doses daily was begun on this date and 500 cc. of whole blood were given. A second sternal bone marrow revealed a total nucleated cell count of 180,000/cu. mm. with 93.5 per cent myeloblasts and promyelocytes. Mature granulocyte cells showed no significant increase in either the peripheral blood or bone marrow.

Weakness, pallor and profound malaise developed concurrently with the fall in the white blood cell count, and a perirectal abscess was incised and drained. There was a progressive irregular rise in the white blood cell count (Fig. 3) to 61,300/cu. mm. with 88 per cent myeloblasts. Death occurred three weeks after aminopterin had been discontinued.

At autopsy the liver was enlarged and infiltrated with leukemic cells. The spleen contained solid sheets of tumor cells and the gallbladder, kidney, pancreas and viscera were infiltrated. In three locations in the small intestine the mucosa was infiltrated by three fungating, ulcerated, indurated masses, each of which was 2 cm. in diameter. Massive infiltration of all layers of the ileum with tumor cells was noted and a necrotic, ulcerated surface extending 2 cm. was present. There was marked involve-

ment of mediastinal and retroperitoneal nodes. Vertebrae and sternal marrow showed marrow spaces filled with early white cells, having large round nuclei and possessing nucleoli. Band forms and a few polymorphonuclear cells were seen. Megakaryocytes were greatly reduced in number.

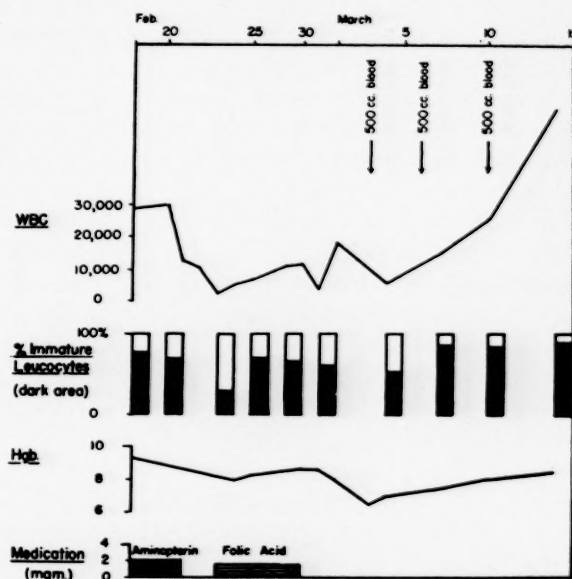


FIG. 3. Patient with acute myeloblastic leukemia who showed a reduction in total leukocytes in the peripheral blood following aminopterin therapy. The number of blast cells was only slightly lessened and the bone marrow was unchanged.

CASE IV. B. A. H., a white female aged thirty-one, was admitted to St. Vincent's Hospital in Bridgeport, Connecticut, on June 11, 1948. A two-month history of extreme pallor following a febrile illness and rash was given. Physical examination revealed pallor, scattered petechiae, cervical lymphadenopathy and hepatosplenomegaly. The admission peripheral blood count was as follows: erythrocytes 1.97 million, leukocytes 39,950/cu. mm. with 23 per cent blast forms, and 76 per cent small lymphocytes. In differential smears on the following three days the blast count ranged from 61 to 69 per cent with marked fluctuations in the total white blood cell count. Sternal marrow aspiration revealed 28 per cent lymphoblasts, 58 per cent early lymphocytic forms and 5 per cent small lymphocytes. A diagnosis of acute lymphoblastic leukemia was made.

The patient was started on aminopterin, 0.5 mg. intramuscularly daily, and liver extract, 20 units per week. At the end of seven days the total white blood count had fallen to 17,800/cu.

mm. with 63 per cent blasts. A total of 2.5 mg. of aminopterin was given during the next four days, resulting in a continued fall in leukocytes to 3,900/cu. mm. with 6 per cent blasts, 15 per cent early lymphocytes and 73 per cent small lymphocytes. There was little change in the size

peripheral blood and bone marrow were markedly reduced during the entire period of study. (Fig. 4.)

Postmortem examination disclosed diffuse petechial hemorrhages and purpura over the entire body with a hematoma of the left lower

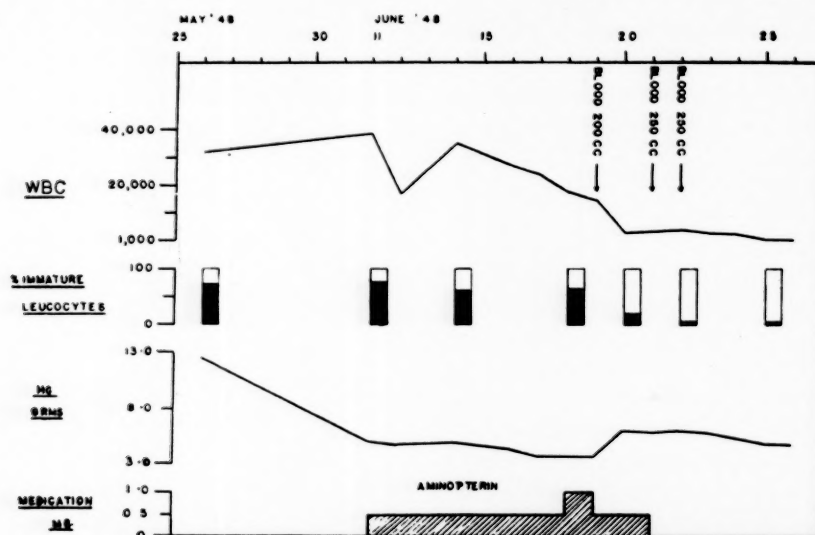


FIG. 4. Patient with acute lymphoblastic leukemia who showed a reduction in total number of leukocytes and blast cells in the peripheral blood following aminopterin therapy. The bone marrow became completely hypoplastic; bleeding from gastrointestinal tract and purpura were observed.

of the lymph nodes, liver or spleen. The red blood cell count and hemoglobin were unchanged. Two transfusions of 250 cc. of whole blood were given on the ninth and eleventh hospital days. A second bone marrow aspiration done on the twelfth hospital day revealed a blast count of 55 per cent, early lymphocytic forms 25 per cent and small lymphocytes 15 per cent. Because of fever, marked fall in the peripheral blood count and the poor clinical condition of the patient, aminopterin was discontinued after the patient had received 6.0 mg. over a period of eleven days. Bloody diarrhea developed on the thirteenth day and fever to 105°F. persisted. Penicillin, 200,000 units daily, was started. The peripheral total white blood cell count continued to fall and four days after the last dose of aminopterin reached 1,100/cu. mm. with 6 per cent blasts, 76 per cent small lymphocytes and no granulocytes. The leukocytes failed to rise and the patient died on the eighteenth hospital day. A sternal marrow on the day of death revealed marked hypoplasia. Differential smears showed 5 per cent blasts, 60 per cent small lymphocytes, 1 per cent mature granulocytes and 21 per cent normoblasts. Platelets in the

lip. Similar hemorrhagic extravasations were found throughout the peritoneum, pericardium and parietal pleura. Extensive bleeding into the submucosa of the entire small intestine with irregular ulceration of the mucosa was present. The non-ulcerated portion of the mucosa was covered by a yellowish green exudate. Petechial hemorrhages of the lungs, gastric mucosa, surfaces of the kidneys and mucosae of renal pelvis, ureters and bladder were noted. Microscopic examination confirmed these gross findings of diffuse hemorrhage into the organs enumerated. The bone marrow appeared hypoplastic.

CASE V. S. L., a white male aged thirty-nine, was admitted to the New York Hospital because of fever and weakness of three months' duration and vomiting for two months. At the onset, which was acute, pain developed in the left axilla, and the patient had fever of 103°F., cough and blood-streaked sputum. This was followed with dyspnea. Paracentesis of the chest cavity was performed which relieved his symptoms temporarily. He had a gradual recurrence of symptoms with daily elevation of temperature up to 101°F., profuse sweating, anorexia, sour

eructations, fullness of abdomen after eating, low back pain, occasional vomiting, bloody stools and loss of 20 pounds. The past and family histories were non-contributory. Physical examination revealed a pale, chronically ill, poorly nourished male who showed evidence of weight loss. Respirations were rapid and shallow. Positive findings included an enlarged node 2 cm. in diameter in the right upper anterior cervical region, signs of fluid in the left chest cavity, apical systolic murmur, a large, hard, nodular mass in the right upper quadrant of the abdomen extending down to the level of the umbilicus, and external and internal hemorrhoids.

Laboratory findings included urinalysis which showed albumin 2 plus, occasional red blood cells, white blood cells, hyaline and granular casts. The blood count was hemoglobin 10.5 gm., erythrocytes 3.2 million, leukocytes 8,000, with a normal differential distribution. X-ray examination of the chest revealed a left hilar mass extending into the parenchyma of the left lung, a mass in the right lower lobe and fluid in the left base posteriorly. Biopsy of the right cervical node showed lymphosarcoma.

During the first three weeks in the hospital the patient had a fever ranging between 38° and 40°C. A course of nitrogen mustard (0.4 mg./kg.) produced no change in the clinical condition or temperature. Radiation of the right chest and mediastinum was followed by a fall of leukocytes to 600/cu. mm., the differential count remaining unchanged. During this period blood transfusions were administered as indicated. The white blood cells gradually rose to 6,000/cu. mm. The patient's course was continuously downward and there were fever and progressive cachexia. Bone marrow aspiration showed normal total cellularity and differential counts. Aminopterin, 4 mg., was given intramuscularly daily for four days. The patient's condition became critical. His temperature rose to 41°C. A thick gray ulcer and membrane were found in the posterior pharynx and on the buccal mucosa of the cheeks and lips. A necrotic, red, pustular rash appeared over the legs and lower body. The leukocytes fell to 600/cu. mm. with no change in the differential count. The bone marrow was markedly hypoplastic. During the brief period of aminopterin therapy the abdominal mass appeared to decrease in size.

Postmortem examination revealed a huge retroperitoneal mass in which the adrenal

glands, kidneys, upper portions of the ureters, pancreas, aorta and inferior vena cava were imbedded. The liver, duodenum and right colon were adherent to this mass. Nodules of neoplastic tissue were found in both kidneys, mediastinum, hilar and cervical nodes and the body of the first lumbar vertebra. The pleural surfaces of both lungs were thickened and 150 cc. of cloudy yellow fluid were found in each of two pockets in the right chest cavity. The liver and spleen were normal in size. Shallow ulcers and petechiae were found in the mucosa of the colon. Microscopic study of the lymph nodes and tumor masses in the organs named on gross examination revealed a marked overgrowth of densely packed, uniform cells resembling lymphocytes. In some areas there was necrosis of tumor tissue. Sections of the colon disclosed congestion and hemorrhage in the mucosa and edema of the submucosa. The bone marrow was hypoplastic and fatty.

COMMENTS

Analysis of the data of these five cases indicates that there was no beneficial effect in any of the patients treated. In no instance was there improvement in the hemoglobin, erythrocytes or platelets. The reduction in leukocytes and immature forms in two persons (J. K. and H. K.) was not reflected in the clinical condition of either. In the remaining three patients leukopenia developed with no subjective response. The bone marrow was unchanged in two patients, somewhat less cellular in one (but still blastic) and markedly hypoplastic in the remaining two. The typical oral lesions of a folic acid antagonist developed in two of the cases. This consisted of thick, white adherent membranes over the labial, buccal or pharyngeal mucosae. In one patient (J. K.) the membrane disappeared when the drug was discontinued but recurred when a second course of therapy was given. Gastrointestinal lesions manifested clinically by oral or rectal bleeding and at autopsy by ulceration of intestinal mucosa were observed in three of the patients. (In one (B. A. H.) a white membrane covered portions of the intestinal mucosa.) In all instances this symptom presaged imminent death. The skin lesions in this group con-

sisted of hemorrhagic infiltration of the skin in two of the patients. No alopecia was found in this small group. In one case the liver increased in size. No other changes were noted in size of liver, spleen or nodes. The abdominal masses in one person seemed to regress slightly. In no instance was there any indication that the drug improved the clinical course of any patient. Toxic manifestations in one form or another were found in all cases.

CONCLUSIONS

1. Four patients with acute or subacute leukemia and one with lymphosarcoma were treated with aminopterin in doses varying from 0.5 to 5 mg./day.

2. There was no clinical or significant hematologic improvement noted in any of the cases.

3. Toxic manifestations were evident in all patients. These included one case of severe leukopenia, two instances each of hypoplasia of bone marrow, stomatitis and skin lesions, and three examples of gastrointestinal dyscrasia.

Acknowledgment: The authors are indebted to Dr. John Lo Cricchio of St. Vincent's Hospital, Bridgeport, Conn., who performed the necropsy in Case IV.

REFERENCES

1. SEEGER, D. R., SMITH, J. M., JR. and HULTQUIST, M. D. Antagonist for pteroyl glutamic acid. *J. Am. Chem. Soc.*, 69: 2567, 1947.
2. LITTLE, P. A., SAMPATH, A., PAGANELLI, V., LOCKE, E. and SUBBAROW, Y. The effect of folic acid and its antagonists on Rous chicken sarcoma. *Tr. New York Acad. Sc.*, 10: 91-98, 1948.
3. LITTLE, P. A., OLESON, J. J. and SUBBAROW, Y. The effect of nutrition on the tumor response in Rous chicken sarcoma. *J. Lab. & Clin. Med.*, 33: 1139-1143, 1948.
4. MOORE, A. E., SOCK, C. C., SUGIURA, K. and RHODES, C. P. Inhibition of development of sarcoma 180 by 4-amino, N-10 methyl pteroyl glutamic acid. *Proc. Soc. Exper. Biol. & Med.*, 70: 396-398, 1949.
5. SCHOENBACH, E. B., GOLDIN, A., GOLDBERG, B. and ORTEGA, L. G. Effect of folic acid derivatives on sarcoma 180. *Cancer*, 2: 57-64, 1949.
6. HIGGINS, G. M. and WOODS, K. A. The effect of the folic acid antagonist, 4-amino pteroyl glutamic acid on the growth of transplanted mammary tumors in C₃H mice. *Proc. Staff Meet., Mayo Clin.*, 24: 238-242, 1949.
7. THIERSCH, J. B. and PHILIPS, F. S. Folic acid and antagonists in neoplastic disease. *Am. J. M. Sc.*, 217: 575-585, 1949.
8. FRANKLIN, A. L., BELT, M., STOKSTAD, E. L. R. and JUKES, T. H. Biological studies with 4-amino, 10-methyl, pteroyl glutamic acid. *J. Biol. Chem.*, 177: 621-629, 1949.
9. BURCHENAL, J. H., BURCHENAL, J. R., KUSHIDA, M. N., JOHNSTON, S. F. and WILLIAMS, B. S. The effect of 4-amino pteroyl glutamic acid and 4-amino, N-10 methyl pteroyl glutamic acid on transplanted mouse leukemia. *Cancer*, 2: 113-118, 1949.
10. WEIR, D. R., WELCH, A. D. and HEINLE, R. W. Effect of an antagonist of pteroyl glutamic acid on the leukemia of AK mice. *Proc. Soc. Exper. Biol. & Med.*, 71: 107-111, 1949.
11. MEYER, L. M. Use of folic acid derivatives in the treatment of human leukemia. *Tr. New York Acad. Sc.*, 10: 99-102, 1948.
12. MEYER, L. M., FINK, H., RITZ, N. D., ROWEN, M. J. and SAWITSKY, A. Folic acid derivatives in the treatment of human leukemia. *Proc. Am. A. Cancer Research*, March 13, 1948.
13. FARBER, S., DIAMOND, L. K., MERCER, R. D., SYLVESTER, R. F., JR. and WOLFF, J. A. Temporary remission in acute leukemia in children produced by folic acid antagonist, 4-amino pteroyl glutamic acid. *New England J. Med.*, 238: 787-793, 1948.
14. FARBER, S. Some observations on the effect of folic acid antagonists on acute leukemia and other forms of incurable cancer. *Blood*, 4: 160-167, 1949.
15. MEYER, L. M., FINK, H., SAWITSKY, A., ROWEN, M. and RITZ, N. D. Aminopterin (a folic acid antagonist) in the treatment of leukemia. *Am. J. Clin. Path.*, 19: 119-126, 1949.
16. PRICE, M. and ALT, H. Treatment of acute leukemia with aminopterin (4-amino pteroyl glutamic acid). *J. Lab. & Clin. Med.*, 33: 1642-1643, 1948.
17. STICKNEY, J. M., HAGEDORN, A. B., MILLS, S. D. and COOPER, T. Changes in blood and bone marrow in acute leukemia induced by aminopterin. *J. Lab. & Clin. Med.*, 33: 1481, 1948.
18. NELIGH, R. B., BETHELL, F. H. and MEYERS, M. C. Effect of a pteroyl glutamic acid inhibitor in leukemia and related disorders. *Am. J. Med.*, 5: 624, 1948.
19. BERMAN, L., AXELROD, A. R., VONDER HEIDE, E. C. and SHARP, E. A. Use of a folic acid antagonist in chronic leukemia. *Am. J. Clin. Path.*, 19: 127-133, 1949.
20. TAYLOR, S. G., SLAUGHTER, D., PRESTON, F. W., CRUMVINE, J. and HASE, G. Effect of antifolic acid derivatives on patients with far-advanced carcinomatosis. *J. Lab. & Clin. Med.*, 33: 1645-1646, 1948.

The Continuing Hazard of Bromide Intoxication*

HORACE H. HODGES, M.D. and MONROE T. GILMOUR, M.D.

Charlotte, North Carolina

WE continue to observe a relatively high incidence of bromide intoxication in spite of the fact that the pharmacologic properties of the bromide ion are well known to most physicians. The purpose of this paper is to reemphasize the hazard of the use of bromide preparations, to ascertain some of the reasons for the continuing high incidence of bromism and to suggest measures to decrease the hazard.

Between January 1, 1947, and December 31, 1949, in our private office and hospital practice we encountered thirty-six patients who exhibited symptoms and signs of bromide toxicity. Twenty-two were females and fourteen were males. Ages varied from twenty-four to seventy-one years. Various types of personalities and modes of intoxication were observed.

Twelve patients secured and ingested a bromide-containing drug on their own volition without medical advice. Seven of these patients were chronic alcoholics. The others were emotionally unstable. None of this group was cognizant of the cumulative and intoxicating properties of the drug. Two patients developed symptoms of bromide intoxication through the continued use, without medical advice, of a drug preparation the contents of which were not known to them. Seventeen patients (almost half of this series) developed bromism directly as the result of prescriptions given them by physicians. In the remaining five patients there was no admission of bromide intake even though the blood level was high. These patients probably took bromide voluntarily without medical advice.

Clinical Manifestations. The symptoms and signs of bromism in this group of patients (Table 1) were similar to those adequately described in numerous papers and textbooks.¹⁻⁵ Most constantly observed were dizziness and/or unsteadiness. True

TABLE I
CARDINAL MANIFESTATIONS OF BROMISM

	Number	Per cent
Dizziness and/or unsteadiness	28	77
Confusion	20	57
Memory loss	19	54
Hallucinations	8	23
Acne	5	14
Slurred speech	5	14

rotary vertigo was not frequent but the subjective sensation of "swimmy-headedness" was a common complaint. This was more significant when associated with ataxia or unstable stance and gait. Subjective and objective mental confusion with general dulling of the intellect likewise was a common finding. Diminution of memory was noted in over half of the patients. Actual hallucinations or delusions severe enough to suggest a psychosis were not uncommon, particularly in cases with the higher blood bromide concentrations. Signs of organic neurologic disorder other than disturbed gait and stance were not common. Slurred speech, fatigue, weakness and other general symptoms were frequent complaints but could not be attributed always to the bromism. Acneform skin lesions occurred

* From The Gilmour-Hodges Clinic, Charlotte, N. C.

in a minority of patients and no other type of dermatitis was seen in this group.

The diagnosis of bromism is easy. It depends upon the suspicion of its presence and a blood bromide determination. The possibility of its occurrence should be con-

TABLE II	
DIFFERENTIAL DIAGNOSIS	
Brain tumor, frontal lobe	
Central nervous system syphilis	
Psychosis	
Schizophrenia	
Manic-depressive	
Toxic	
Psychoneurosis	
Vestibular disease	
Cerebral arteriosclerosis	
Barbiturate addiction	
Early uremia	

sidered in all cases in which patients exhibit the foregoing manifestations, and blood bromide determinations should be made regardless of admission of intake. Listed in Table II are some of the most common conditions with which bromism may be confused. It is frequently wise to withhold making one of these diagnoses until the blood bromide concentration has been found normal. In the instance of the psychoses there are many reports of a high incidence of bromism among patients committed to hospitals for the insane.⁶ Two of the patients reported in this paper were referred to us for a preliminary general medical survey prior to a consideration of commitment to the State Hospital for the Insane. Certainly any patient who is confused or unsteady and who is suspected of having a psychosis, organic brain lesion, other drug addiction or alcoholism deserves a blood bromide determination. We have come to the belief that the blood bromide test would be of more value to the internist than is the serologic test for syphilis. We see more bromism than we do syphilis.

Relation of Blood Level to Severity of Symptoms. In general, the higher the blood bromide concentration the more severe were the symptoms. This was most consistently true with regard to hallucinations, confusion, memory loss and skin eruptions. Other reports, however, have indicated that

the presence of acneform skin eruptions was not related to the height of the blood bromide level but rather to individual sensitivity.²⁻⁴ The general condition of the patient seems to influence the level at which symptoms appear.⁴ Elderly, arteriosclerotic and malnourished patients exhibited toxic symptoms at lower blood concentrations than did younger, healthier patients. Thus eight of our patients exhibited definite symptoms with a bromide blood level of 100 mg. per cent or less at the time of the test. Some of these levels may well have been higher a few weeks previously in instances in which intake had ceased some time before the test. Sixteen of our patients were found to have a blood bromide level between 100 mg. per cent and 200 mg. per cent. Six patients had levels between 200 mg. per cent and 300 mg. per cent. The determination in four patients exceeded 300 mg. per cent. One patient had a level of over 500 mg. per cent. The average blood concentration for this group of thirty-six patients was 154 mg. per cent.

COMMENT

It is frequently stated that the critical level for development of symptoms of bromide intoxication is 150 mg. per cent. It would be better to say that the *average* level at which signs are manifested is 150 mg. per cent. The characteristics of the manifestations in our patients and their gradual disappearance with the cessation of bromide intake leaves little doubt but that they resulted from bromide toxicity even when blood bromide levels were lower than 150 mg. per cent.

We have been unable to find much data on the speed of development of signs and symptoms of bromism. Obviously the rapidity of development of symptoms must be directly proportional to the rate of intake and inversely proportional to the rate of excretion. The danger in the use of bromides resides in the fact that excretion is so much slower than intake. It is stated that as little as 2.0 gm. of bromides per day in an elderly patient may produce intoxication within a few weeks.⁷ We have observed the develop-

ment of a blood bromide level of 108 mg. per cent in nine days in an otherwise healthy middle aged woman from slightly less than 6 ounces of elixir of triple bromides. We have also observed an increase in the blood bromide level from 100 mg. per cent to 305 mg. per cent within a period of twelve days. This gives us some idea of how rapidly toxic symptoms may be produced. Actual intoxication is said to begin when 23 to 25 per cent of the body chlorides has been replaced with bromide. Forty per cent replacement is said to be fatal.^{4,8}

The continuing high incidence of bromism is the result of a combination of factors. First, physicians still prescribe the drug with inadequate precautions against prolonged use or patients ignore the advice. Second, there is grossly inadequate legislative control over the sale of bromide-containing preparations. Third, patients generally are aware that bromides have a sedative effect but are not aware of the cumulative and toxic properties.

Adequate legislative control is necessary if the hazard of bromide intoxication is to be overcome. Bromide-containing preparations should be sold only on doctors' prescriptions. It should be unlawful for proprietary drugs and patent medicines to contain bromide and be sold indiscriminately. Furthermore, once legislative control has become established it will continue to be important for the doctor to remember the danger when prescribing bromides. There are so many non-cumulative sedatives that the use of bromides could actually be abandoned. We believe that there is rarely justification or necessity for the use of bromides.

Specific treatment is relatively simple and is directed at stopping bromide intake and increasing the rate of bromide excretion. Sodium chloride should be given orally and parenterally in large amounts. The oral dose of salt varies with the patient's tolerance but lies between 4 and 8 gm. daily. In addition to this, 1 to 2 L. of normal saline may be given parenterally daily. In cardiac decompensation, severe hypertension, edem-

atous states, etc., ammonium chloride may be substituted for sodium chloride. The administration of adrenal cortical hormone has been suggested and used but is not necessary.⁵

Other general measures in the over-all therapy of the patient are important. Sedation usually must be maintained for a time, using barbiturates, chloral hydrates, paraldehyde, etc. The importance of maintenance of good nutrition and psychotherapy is obvious.

Improvement usually is prompt, beginning about seven days after initiation of the full treatment program. The blood level falls approximately 50 per cent each seven to ten days with large chloride intake. For instance a blood bromide level initially 300 mg. per cent would be expected to fall to 150 mg. per cent within the first seven to ten days and from 150 mg. per cent to 75 mg. per cent within the next seven to ten days.

Some think it dangerous to administer large amounts of chloride to patients with diminished renal function on the theory that bromide is displaced from various tissues more rapidly than it can be excreted, allowing the blood concentration to rise. This we have not observed.

SUMMARY

1. Bromide intoxication remains a hazard for the following reasons: (1) The drug is cumulative in its action. (2) The physician continues its use. (3) There is inadequate legislative restriction to its sale with or without a doctor's prescription.

2. The important diagnostic manifestations are unsteadiness, dizziness, mental confusion, memory loss and psychotic symptoms, in the absence of signs of organic disease.

3. The diagnosis is easily made by a blood bromide determination if one is suspicious enough to have this test made.

4. Therapy is simple and consists of displacing the bromide with chloride.

5. Adequate control of the use of bromide-containing preparations both at the

legislative level and at the level of the individual physician is essential to elimination of the hazard.

REFERENCES

1. BENDER, JOHN R. Bromide intoxication. *North Carolina M. J.*, 8: 357, 1947.
2. NETHERTON, EARL W. Nodular papillomatous bromoderma. *Cleveland Clin. Quart.*, 12: 19, 1945.
3. GRUBER, CHAS. M. The Cyclopedia of Medicine, Surgery and Specialties, 3: 414, 1941.
4. SENSENBACH, WILLIS. Bromide intoxication. *J. A. M. A.*, 125: 769, 1944.
5. KRACKE, ROY R. and PLATT, WM. R. Bromide intoxication from prolonged self medication with B.C. headache powder. *J. A. M. A.*, 125: 107, 1944.
6. WAGNER, C. P. and BUNBURY, D. E. Incidence of bromide intoxication among psychotic patients. *J. A. M. A.*, 95: 1725, 1930.
7. DAX, E. CUNNINGHAM. Overdosage with bromides; report on 59 cases. *Brit. M. J.*, 2: 226-227, 1946.
8. NORBURY, F. G. Hazards in the use of sedatives: bromide intoxication. *Illinois M. J.*, 90: 223, 1946.

Criteria for the Management of Neurosyphilis*

BERNHARD DATNER, M.D., EVAN W. THOMAS, M.D. and LOPO DE MELLO, M.D.

New York, New York

IT has long been recognized that syphilis of the central nervous system may produce signs and symptoms which simulate a great variety of neurologic disorders of non-syphilitic origin. On the other hand, even such classic clinical syndromes as general paresis and tabes dorsalis are not necessarily due to syphilis, as indicated by the terms pseudoparesis and pseudotabes. Consequently, both syphilologists and neuropsychiatrists have long relied on spinal fluid examinations for diagnosing neurosyphilis.

Although neurologic examination of every patient with neurosyphilis is of course essential, it is important to recognize that the physical findings are not the most reliable guide to the activity of the syphilitic process since the signs and symptoms may persist long after active infection has ceased. Late lesions of syphilis are always destructive and they heal with scar tissue. When extensive damage has occurred at some site in the central nervous system and scar tissue has formed, it is futile to expect antisyphilitic treatment to restore normal function except in certain cases in which the function of permanently destroyed nerve cells may be compensated for by other cells. The internist always attempts to distinguish between active and healed tuberculosis and between active and inactive rheumatic heart disease. In doing so he does not depend solely on the physical examination or symptoms. The same problem confronts the physician treating syphilis. Is the syphilis active?

In the case of neurosyphilis, with possible rare exceptions, a reliable answer to this question can be obtained from the spinal fluid examination. We first outlined our

concepts regarding the interpretation of spinal fluid examinations for syphilis in 1942.¹ Although the opinions stated in that article were not immediately accepted by all workers in the field, we have had no reason to alter them during the past eight years. Additional experience with the newer technics for quantitative complement fixation tests, total protein determinations and colloidal gold tests have only confirmed our concepts which can now be amplified and further clarified.

Spinal Fluid Tests as Indicators of the Activity of Neurosyphilis. Briefly stated, we have found that the spinal fluid examination, with possible rare exceptions, is a reliable indicator of the activity of a syphilitic process in the central nervous system. A positive specific test for syphilis (complement fixation or flocculation test) does not in itself prove an active infection because we have abundant proof that reagin can be demonstrated in both blood and spinal fluid for years after the infection has been arrested or even cured. It is true that when serial quantitative specific tests for syphilis are made on spinal fluids, examined at intervals of three to six months, decreasing complement fixation titers are an indication of inactivity; but a single test, regardless of the amount of reagin present, does not prove activity. When, however, a positive specific test for syphilis is associated with increased cells (chiefly lymphocytes) and increased total protein in the spinal fluid, we have definite evidence of active infection.

The claim has been made that numerous patients, untreated for syphilis, have been observed to have positive spinal fluid Was-

* From the Departments of Neurology, Medicine and Dermatology and Syphilology, New York University—Bellevue Medical Center, and the Departments of Neurology, Medicine and Dermatology and Syphilology, Third Medical Division, Bellevue Hospital, New York, N. Y. Aided by grants from the United States Public Health Service.

sermann tests and normal cells and protein. In our experience such findings in untreated neurosyphilis are rare. When they occur the infection may be very low grade or a spontaneous arrest may have occurred. We do not advise that such untreated patients be observed without treatment because the cell count might have been in error or the relatively quiescent infection might subsequently exacerbate. However, we have found that the great majority of untreated patients who have positive spinal fluid Wassermann tests also have pleocytosis and they usually have increased total protein as well.

Evaluation of Treatment by Spinal Fluid Examinations. Following treatment of active neurosyphilis certain eventualities may occur. (1) The infection may be permanently arrested. In this case the cell count should be normal (not more than four cells per cu. mm.) within six months after treatment and the total protein, if originally increased, should show a decrease in amount. Subsequent spinal fluid examinations at six-month intervals should show continued normal cell counts and a gradual fall in protein values, quantitative specific tests for syphilis and quantitative colloidal tests. Very high total protein values should show a marked diminution within one year after treatment, but the results of the complement fixation and colloidal tests may not become completely normal for many years after treatment. (2) Following treatment the infection may be temporarily arrested only to relapse to renewed activity within two years. In this case increased cell counts temporarily become normal and there is a temporary drop in other abnormal quantitative tests but, as the infection again becomes active, pleocytosis and increases in other quantitative tests occur. Such findings represent a relapse of a temporarily arrested infection. In our experience we have not observed a relapse, as demonstrated by spinal fluid examinations, more than two years after treatment. This observation has been questioned by some authorities² but it is based on long experience in the follow-up

of many hundreds of treated cases. We believe that relapses of spinal fluid findings reported as occurring more than two years after treatment might be due to reinfection but we have had no experience with such cases. Our observation that spinal fluid examinations have shown no evidence of relapse more than two years after treatment has been confirmed by other reports in the literature.³⁻⁵ (3) The third possibility following treatment is failure to arrest the infection even temporarily. In this case cell counts do not become normal. Continued pleocytosis more than six months after treatment with no marked drop in other quantitative spinal fluid tests is definite proof of a continued active inflammatory or degenerative process in the central nervous system.

Thus, inactive neurosyphilis is demonstrated in the spinal fluid by normal cell counts and gradually falling values in other tests.

Treatment of neurosyphilis with bismuth and arsenicals may cause temporary normal cell counts, but in our experience over 50 per cent of patients treated for active neurosyphilis with large amounts of metal therapy have shown pleocytosis and rising values in other tests within one year after metal therapy was stopped. Consequently, we advise penicillin therapy for all neurosyphilitics who have had recent treatment with metal therapy, regardless of the presence or absence of pleocytosis.

COMMENT

Evaluation of the status of neurosyphilis by means of spinal fluid examinations has been criticized by numerous authorities because no clinical improvement was obtained in some patients whose spinal fluid findings indicated arrest of the syphilitic process or because some patients showed progression of clinical signs and symptoms in the presence of a normal spinal fluid. It has been argued that the patients' condition is what matters and not the results of laboratory tests.⁶ However, failure to restore normal function to permanently damaged

tissue does not prove continued activity of the disease process. Every cardiologist would like to restore the fibrosis of a myocardial infarct with functioning muscle but he knows that this is impossible and he recognizes that progressive signs of a lowered cardiac reserve following an infarct do not prove that additional infarcts are occurring. Patients who have had a severe syphilitic infection of the central nervous system have much scar tissue and a lowered central nervous system tissue reserve. Even though the syphilitic infection may be cured, subsequent insults such as infections, arteriosclerosis and trauma may produce symptoms and signs which give the impression that the syphilitic infection is progressive. An old tabetic patient with normal spinal fluid findings may become incontinent when cystitis is superimposed upon a cord bladder. Lightning pains may occur in arrested tabes from any one of a great variety of causes other than active syphilis. Antisyphilitic treatment will accomplish nothing in such cases, with the qualification that when penicillin or other antibiotics are used, infections other than syphilis may be cured with resulting benefit to the patient. Intercurrent diseases, emotional strain and fatigue may alter the behavior of such individuals even though the syphilitic infection is arrested or cured. The varying behavior of a treated paretic does not prove reactivation of a syphilitic encephalitis.

The experience of Bruetsch,⁷ Gammon and coworkers,⁸ and Smith and Morais,⁹ who found no evidence of active inflammation in postmortem examination of patients with "inactive spinal fluids," support our observation. One of us (B. D.) reported on malaria-treated paretics with "inactive spinal fluids" who exhibited transient psychotic episodes caused by trauma, acute infection, operative procedure and alcohol intoxication.¹⁰

TREATMENT OF NEUROSYPHILIS

Abundant evidence now exists that penicillin therapy is the treatment of choice for all types of neurosyphilis. Practically all

authorities are now agreed that injection of from 6 to 10 million units of penicillin over a period of eighteen to twenty-one days has produced satisfactory results as evidenced by spinal fluid examinations in over 90 per cent of treated cases. Intramuscular injections of penicillin are preferred. Intrathecal penicillin therapy is difficult and dangerous and, from the reported data, it has given no better results than intramuscular injections.

We have found in the treatment of over 500 cases of active neurosyphilis since April, 1944, that any of the current preparations of penicillin are satisfactory for the treatment of most cases of neurosyphilis. The most convenient preparation now on the market is procaine penicillin G with or without aluminum monostearate. If the aluminum monostearate preparations are used, daily injections are not essential. However, higher blood concentrations of penicillin are obtained if almost daily injections of at least 600,000 units are given. Procaine penicillin G in water or oil without aluminum monostearate gives blood concentrations with higher peaks and sharper drops than when aluminum monostearate is added. There seems to be no advantage in obtaining relatively brief high blood concentrations of penicillin in the treatment of neurosyphilis and the aluminum monostearate preparations have the advantage of maintaining demonstrable concentrations of penicillin in the blood for at least four days after a single injection of from 300,000 to 600,000 units.

In our experience penicillin has proved as effective in producing clinical improvement of neurosyphilis as malaria therapy did during the years when we used fever therapy for all cases of active neurosyphilis. When repeated treatments with large amounts of penicillin fail to restore abnormal cell counts to normal or to reduce other quantitative spinal fluid tests, fever therapy may be tried. However, we have observed only three cases in a series of over 500 in whom repeated courses of increased dosage of penicillin failed to arrest the in-

fection and it is still possible that these three cases will not require fever therapy as one of them has already responded to a fourth treatment with very large amounts of penicillin, and the other two are still under observation after re-treatment.*

and are reported in the 1946 edition of Wadsworth's "Standard Methods:"¹¹

Quantitative Complement Fixation Test. The best quantitative complement fixation test that we know about is that devised by Maltaner and Maltaner of the New York

TABLE 1

Test No.	Date	Blood Complement Fixation	Blood Kahn	Spinal Fluid Complement Fixation	Spinal Fluid Cells	Spinal Fluid Total Protein	Spinal Fluid Colloidal Gold
1*	2/13/42	4+	4+	4+†	225/3	60	5555443211
2	9/7/42	4+	4+	4+†	21/3	35	3344442110
3	2/4/43	4+	4+	4+†	44/3	33	0111222332
4	6/27/43	4+	4+	4+†	5/3	35	2221100000
5	5/29/44	4+	4+	4+†	18/3	48	0111100000
6	10/17/44	4+	4+	4+†	160/3	71	1111100000
7‡	10/30/44	12	8	37	58/3	56	1.5,2,3,6,11,12,15,13,9,6.5 (79)
8	12/4/44	12	8	30	1/3	45	2,3,5,12,13,13,10,9.5,7.5,5.5 (81)
9	2/5/45	9	8	21	8/3	43	2,2.5,3,4.5,7,11,11,11,10,8 (70)
10	8/6/45	3	3	16	8/3	41	1.5,2,3,6,8,9,8,7.5,6,4.5 (56)
11	1/21/46	4	3	13	3/3	31	1.5,2,3,6,7.5,6,5,3.5,2 (44)
12	5/13/46	4	3	6	1/3	31	1.5,2.5,4.5,7,9,9,3.5,6.5,5.5,3.5 (53)
13	10/29/46	2	3	12	3/3	31	2,2.5,3.5,6,8,8.5,7.5,6.5,4.5,2.5 (52)
14	4/18/47	3	3	7	3/3	30	1.5,2.5,4.5,6.5,7.5,7.5,5,4,2.5,2 (44)
15	11/7/47	Negative	Negative	4	6/3	33	1.5,2.5,3.5,6,7.5,8.5,8.5,8.5,6.5,2.5 (55)
16	2/6/48	2	1	6	4/3	31	2,2.5,4.5,8,8.5,7.5,2.5 (52)
17	11/8/48	Negative	1	3	5/3	32	1.5,2.5,4.5,8,9,9.5,8,6.5,4.5 (59)

* Spinal fluid reports of patient treated for taboparesis with tertian malaria followed with ten daily injections of .06 gm. mapharsen in February and March, 1942; re-treated with quartan malaria in October and November, 1942, followed with ten daily injections of .06 gm. mapharsen and then forty injections of a pentavalent arsenical between January and December, 1943; re-treated in October, 1944, with 4,000,000 units penicillin (40,000 units every three hours for 100 doses).

† Prior to October, 1944, the blood complement fixation and Kahn tests are not reported quantitatively; the 4+ tests reported in spinal fluid represent 4+ tests in 0.1 c.c. and more of fluid and the colloidal gold readings are reported according to the old Lange method.

‡ Beginning October, 1944, the blood complement fixation and Kahn tests are reported in units as are the complement fixation tests of the spinal fluid and the new Lange colloidal gold readings.

VALUE OF MODERN TECHNIQS FOR SPINAL FLUID EXAMINATIONS

Since spinal fluid examinations are so essential for the evaluation of neurosyphilis, it is important that the tests be performed reliably, using the most modern technics. Based on our own experience, we advise the following technics which are now routinely used in the New York State laboratories

* Two of these three re-treated patients now have spinal fluid tests indicating inactivity of the syphilitic process.

State laboratory.¹¹ Results of the tests are reported in units made possible by a more exact titration than when complement fixation tests are reported in varying amounts of spinal fluid. If the latter method is used, tests should be done in amounts varying from .05 cc. to at least 0.8 cc.

Cell Counts. These should be made in a 3.2 mm. counting chamber (Fuchs-Rosenthal chamber). If the cells in all of the squares of this chamber are counted, the total will represent the number of cells in

3 cu. mm. of fluid. To indicate that a 3.2 mm. counting chamber has been used, cell counts should be reported in thirds; the numerator indicates the total number of cells counted and the denominator is 3. Counts over $1\frac{2}{3}$ are abnormal.

Total Protein Determinations. These are made by means of turbidity tests using a precipitating reagent such as Exton's reagent. The degree of turbidity can be measured accurately by using an electrophotometer. Unless an electrophotometer is available turbidity tests of total protein are unreliable and inconstant reports will result. Readings with an electrophotometer are checked by standard solutions of protein determined by the micro-Kjeldahl method.

Colloidal Tests. The best colloidal test, in our experience, is the new Lange colloidal gold test.¹¹ With this method color changes in each tube are reported in figures ranging from zero to nineteen instead of from zero to five. A buffered colloidal gold solution is used. Quantitative results are obtained by adding the figures for all ten tubes. The upper limit of normal for the sum of the figures of all ten tubes is forty-five. The highest possible sum would be 190.

We believe that adoption of the newer technics for spinal fluid tests such as used by the New York State laboratories would provide clinicians with much more helpful information than is possible with the older technics.

SPINAL FLUID FINDINGS IN A PATIENT TREATED FOR TABOPARESIS

Table 1 gives the spinal fluid examinations, first with the older and later with the newer technics for complement fixation tests and colloidal gold tests in a taboparetic

who was twice treated unsuccessfully with malaria and who responded well to penicillin.

SUMMARY

1. The need for differentiating between active and inactive neurosyphilis is discussed.

2. Rules for establishing the activity of neurosyphilis by means of spinal fluid examinations are given.

3. The advantages of the New York State laboratory technics for quantitative spinal fluid complement fixation and colloidal gold tests are briefly outlined.

REFERENCES

1. DATTNER, B. and THOMAS, E. W. The management of neurosyphilis. *Am. J. Syph., Gonorr. & Ven. Dis.*, 26: 21, 1942.
2. Book Review of "Syphilis: its course and management." *Am. J. Syph., Gonorr. & Ven. Dis.*, 33: 607, 1949.
3. MACFARLANE, W. V. The treatment of neurosyphilis with penicillin. *Newcastle M. J.*, 23: 73, 1948.
4. MARTIN, J. P. The treatment of neurosyphilis. *Practitioner*, 162: 361, 1949.
5. SEZARY, A. Rémarques sur le traitement de la paralysie générale. *Presse méd.*, 56: 836, 1948.
6. GOLDMAN, D. Neurosyphilis treated with penicillin. *J. A. M. A.*, 141: 431, 1949.
7. BRUETSCH, W. L. Penicillin or malaria therapy in the treatment of general paralysis. *Dis. Nerv. System*, 10: 368, 1949.
8. GAMMON, G. D., LEWEY, F. H., DILLON, H., SCHWARZ, G. and STOKES, J. H. Pathological Observations in Penicillin Treated Neurosyphilis. Symposium on Current Progress in the Study of Venereal Diseases, Federal Security Agency, Washington, 1949.
9. SMITH, R. H. F. and MORAIS, DE V. Histopathological findings in general paresis after penicillin treatment: report on 4 cases. *J. Ment. Sc.*, 94: 70, 1948.
10. DATTNER, B. Über interkurrente psychotische Reaktionen bei remittierten Paralytikern. *Wien. klin. Wchnschr.*, 50: 337, 1937.
11. WADSWORTH, A. B. *Standard Methods*. Baltimore, Md., 1946. The Wilkins Co.

Review

Newer Concepts of the Role of Sodium in Disease*

T. S. DANOWSKI, M.D.

Pittsburgh, Pennsylvania

IN a preceding review the more recent additions to our knowledge of body potassium were discussed with especial emphasis on changes in the extracellular and cellular stores of that electrolyte.¹ A comparable evaluation of newer sodium data is now presented together with an attempt to integrate previously known and newly found interrelationships of these two important body cations.

Until recently it has been customary to look upon sodium as an electrolyte without specific effects such as those which accompany changes in the stores and body fluid concentrations of potassium. This has been true even though no other electrolyte in body fluids, inside or outside of cells, is present in as high concentrations. Sodium exerts almost one-half of the osmotic force attributable to electrolytes in the extracellular fluid. Furthermore, it is by no means excluded from cells. As in the case of potassium the forces which condition the sodium content of the cells and of their environment have not been completely defined. There is nonetheless a considerable knowledge of factors which influence the behavior and the effects of this cation.

Extracellular Sodium: Factors in Maintenance of a Normal Concentration. In health sodium levels in serum are maintained within the range of 134 to 141 milliequivalents per liter despite large variations in the intake of this electrolyte.² This is accomplished by suitable adjustments in renal excretion. On the other hand, if the intake is reduced to

zero, the loss of sodium in the urine after a number of days essentially ceases.³⁻⁵ It has long been known, of course, that variations in the urinary excretion of this electrolyte are related in part to adrenal cortical activity.⁶⁻¹¹ More recently it has been shown that with an increased load of sodium presented to the kidneys for excretion the zona glomerulosa of the adrenal cortex decreases in size; on the other hand, this portion of the adrenal hypertrophies during pronounced salt restriction.¹³⁻¹⁶ These changes are presumably related to a decrease and an increase, respectively, in the output of DOCA-like steroids. These compounds increase the tubular reabsorption of sodium from the glomerular filtrate.¹⁷ In the case of potassium an opposite series of histologic changes and effects is present. At times, therefore, an increase in the concentration of urinary sodium may be associated with a diminution in the excretion of potassium.¹⁸⁻¹⁹ The actual stimuli which induce these changes in adrenal cortical activity are not known, but it is probable that they are related to the total amount and the concentration of electrolytes. It should be pointed out that this is an oversimplified version of the role of adrenal cortex in renal function. It omits from consideration the circulatory effects of the steroids.²⁰ Definition of the probable interrelationships is further complicated by the antagonism of the oxy-steroids to the urinary salt effects of the desoxysteroids.²¹⁻²³ The adrenal cortex is, of course, not the sole

* From the Department of Research Medicine and the Children's and Presbyterian Hospitals of the University of Pittsburgh School of Medicine, Pittsburgh, Pa.

hormonal moderator of urinary sodium loss or reabsorption: the hypophysis indirectly influences renal sodium loss through adrenocorticotrophic hormone;²⁴⁻²⁶ products of the posterior part of this gland can modify changes induced by the adrenal steroids;²⁷ deficiency of thyroid hormone results in a deviation of sodium into myxedematous tissues;²⁸ premenstrual changes include increases in body water and sodium.²⁹⁻³¹

Significance of Decreases in Extracellular Sodium. The tendency to maintain intact serum sodium concentrations carries over to disease states. Certain animal and clinical studies indicate that the kidney in the initial phases of sodium loss endeavors to maintain normal extracellular concentrations even though this necessitates a loss of body water.^{32,33} Urine formed at this time is usually of ample volume and, if tubular function is intact, is essentially sodium- and chloride-free.³⁴⁻³⁸ This finding is, of course, a valuable clue pointing to the existence of sodium depletion. Its reliability is further strengthened when it is apparent from the history that the patient has lost sodium from body fluids and yet does not complain of thirst. There is, however, a limit beyond which this urinary adjustment no longer occurs and urinary volume falls off.^{39,40} Serum sodium concentrations can no longer be maintained by this mechanism and hyponatremia appears. With the exception of sweat and urine, fluids lost from the body are in general isotonic; this *per se* should not produce hypotonicity. Therefore its presence points either to (1) losses of sodium without water, as through the use of low sodium fluids in gastric or intestinal lavage, peritoneal irrigation or in an artificial kidney, or (2) losses of sodium with water followed with subsequent replacement of water only. With either category decreases in the bicarbonate content of plasma or actual acidosis may be observed depending on the magnitude of the chloride loss relative to the sodium deficits. It should be emphasized, however, that normal or even high serum sodium concentrations may also be present with decreases in the total amount

of extracellular sodium, depending on the balance of water during periods of sodium loss. In any particular clinical instance it may be difficult or impossible to decide even with the usual laboratory data available the exact state of the extracellular volume and hence of the total amount of sodium. This could be done by determining the volume of distribution of suitable test substances and using it as an index of extracellular fluid volume.⁴¹⁻⁴⁴ This is not a routine procedure and in ill patients, particularly those with circulatory collapse or failure, presents certain special problems. Yet such derangements of water and electrolytes must be corrected even though it may not be possible in each instance exactly to characterize and quantitate the disorder. This is essential since a significant reduction in body sodium is associated with profound circulatory changes. Such a situation can be produced in animals by the intraperitoneal injection of a glucose solution followed in three to six hours by withdrawal of an equivalent volume of fluid from the same space.^{45,46} This results in a loss of sodium and of other solutes which had diffused into the glucose solution into the peritoneal cavity. A movement of extracellular fluid into cells naturally follows as a consequence of the hypotonicity which develops. The diminution of extracellular volume which results is accompanied with deterioration of circulatory efficiency or actual shock.^{47,48} Not only does the plasma volume decline in conjunction with the dehydration of the extracellular space as a whole, but also circulating plasma protein is lost. Although the fate of this fraction is not known, the effects of its loss are clearly evident. A further decline in plasma volume occurs. The hematocrit rises, the circulation slows down, the cardiac output drops and the blood pressure declines. This shock state is quite comparable to that which follows upon trauma or blood loss, and carries with it the same jeopardy to survival. It should be stated at this point that it is as yet not established whether or not an equivalent change induced gradually

over a prolonged period of time necessarily carries with it the same risk of circulatory collapse.

What is the relative importance of the hypotonicity and of the decrease in the total amount of extracellular sodium in the circulatory collapse which follows depletion of sodium? The former derangement can be readily corrected in the experimental situation by inducing a diuresis in which considerable amounts of water but very little sodium are lost. This has been shown to occur following an intravenous injection of urea.⁴⁹ In this way serum levels can be restored to normal but the total amount of sodium is not replaced. It is highly pertinent that the circulatory efficiency does not return to previous levels. If any change is observed, it is toward a further deterioration of cardiovascular function. This clearly suggests that it is not hyponatremia *per se* which is responsible for the shock state accompanying the removal of sodium. On the other hand, re-expansion of the volume of extracellular fluid by means of sodium-free fluids, such as glucose solutions, fails to bring back to normal the cardiac output, circulation time and blood pressure in salt-depleted animals. Saline solutions which reconstitute both the sodium concentrations and the total sodium stores do restore circulatory efficiency.⁴⁹ It should therefore be obvious from the aforementioned facts that any consideration of the extracellular sodium stores must be based on a three-dimensional concept: the *concentration* of sodium, the *volume of extracellular fluid* through which it is distributed and the *total amount* of extracellular sodium must all be taken into account in evaluating any clinical situation.

It becomes especially important therefore to recognize this entity of salt depletion shock in clinical disorders.⁵⁰ A certain proportion of deaths from diabetic acidosis and coma are attributable to it.⁵¹ It is undoubtedly a factor in the fatal outcome of some cases with losses of body fluids, as in diarrhea,⁵²⁻⁵⁵ in vomiting or through fistulas⁵⁶⁻⁵⁹ or burned surfaces.⁶⁰⁻⁶² Similar

hazards are present in patients whose kidneys are incapable of conserving salt, as in Addison's disease and other forms of adrenal cortical insufficiency⁶³⁻⁶⁷ and in some renal disorders.⁶⁸⁻⁷⁰ It is also well to emphasize that sodium depletion can be produced unwittingly during therapy. The subcutaneous injection of salt-free glucose solution is followed with changes in extracellular fluid entirely analogous to those seen when the same solution is given intraperitoneally.^{40,71} Electrolyte pours into the hypodermoclysis pool, hypotonicity ensues and extracellular water moves into the cells. As the injected fluid is absorbed, the electrolytes and water are again restored to the extracellular compartment. This process occurs to a greater or lesser degree with each administration of glucose solution into the subcutaneous tissues. Ordinarily the changes are of insufficient magnitude to affect the circulation adversely. With unusually large clyses, and especially when given rapidly, actual circulatory collapse can be produced in animals or in humans identical with that seen after the intraperitoneal injection and subsequent removal of glucose solution.

The recognition of salt depletion shock calls for prompt therapeutic measures. The experimental evidence is quite helpful in meeting this need. The available data indicate that early reconstitution of the salt stores in the body restores circulatory efficiency completely, or almost completely.⁴⁸ Either isotonic or hypertonic saline solutions may be used for this purpose. If therapy is delayed, it is far less effective or even useless. This is in keeping with the concept that shock which persists without treatment soon becomes irreversible. A definite advantage can be derived, however, from the concomitant use of colloid solutions and saline. It has been demonstrated that a combination of low salt colloid and partial replacement of salt stores restores circulatory efficiency to normal under circumstances in which either alone proves ineffectual.⁷² It is obvious that this combined form of therapy can provide a margin of safety in case of need. Since it is often not possible to

decide whether or not circulatory collapse is irreversible, the patient should receive the benefit of the doubt. Optimal therapy should therefore include not only the replacement of salt deficits but also the administration of whole blood, plasma or other suitable solutions of colloid.

Increases in Extracellular Sodium: Hypertonicity. The physiologic changes which accompany hypertonicity depend upon its degree and upon the mechanisms through which the increases in the concentration of sodium have been produced. The most common cause of elevated extracellular levels of sodium is *simple dehydration*.^{3,37,73-77} Clinically it is encountered most often in patients not receiving water in amounts sufficient to make up for losses through the skin and lungs in the dissipation of heat, i.e., in insensible loss. It may also result from urinary losses of body water in excess of intake as in diabetes insipidus, uncontrolled diabetes mellitus or in hyposthenuric renal diseases. As already mentioned hypertonicity can also be produced by the administration of urea. Comparable or even greater increases in serum sodium concentration will follow, of course, upon the *administration and retention of sodium salts* without sufficient quantities of water to maintain isotonicity. This will not only occur with the injection or ingestion of hypertonic sodium solutions⁷⁸ but also it may develop after the use of hypotonic saline followed with subsequent losses of water without salt. Finally, calculations of transfers between cells and extracellular fluid have often demonstrated movements of sodium out of cells.⁷⁹ If this moiety is not excreted, it will raise extracellular concentrations.

It is obvious that the two major categories of hypertonicity cited are ascribable solely to deficits of water, either absolute or relative. In contrast to the situation in salt depletion the total extracellular sodium stores remain intact or even increase. This distinction cannot be overemphasized in view of the physiologic concomitants. In hyponatremia resulting solely from deficits

of water the circulation is only minimally affected. This has been observed clinically and demonstrated experimentally.^{40,47} The velocity of the circulation and the blood pressure remain essentially unchanged. In some instances the cardiac output declines somewhat. The circulatory collapse so characteristic of salt depletion does not appear even though the extracellular volume is somewhat decreased. The chief manifestations of moderate water deficits with resultant hypertonicity are limited to thirst, oliguria without evidence of renal conservation of sodium and deterioration of cerebral cortical functions.^{4,80,81} With greater degrees of hypertonicity a further group of changes ensues. The circulation is still maintained; the cells, however, become further dehydrated and, in experimental animals, death results from respiratory failure.⁷⁸ A similar course of events presumably occurs in subjects such as castaways who drink and absorb sufficient amounts of undiluted sea water.⁸¹

Fluid therapy in patients with deficits of water should be limited to glucose solutions. Since body salt stores are intact, the administration of saline may even aggravate the dehydration by necessitating larger urine volumes for the excretion of the unneeded electrolyte.⁸²⁻⁸⁵ This is the chief basis for the view that physiologic saline exerts deleterious effects when given post-operatively, but it is obvious that the risk of dehydration by such therapy is not limited to this category of patients.⁸⁶⁻⁸⁸ The risks are even greater in infants with immaturity of renal functions.⁸⁹⁻⁹³

Depletions of body fluid have been discussed in this and the preceding section as if they clearly fell into two categories. This has been done to emphasize the physiologic processes involved and their sequelae. In clinical practice, however, most instances of body fluid loss consist of a mixture of electrolyte and water depletion. Evaluation of the relative proportions of sodium and of water loss is, of course, highly important since administration of sodium-free fluids may aggravate or even produce salt deple-

tion whereas an overenthusiastic use of sodium solution will result in further losses of body water. The several clinical clues which may be of help in identifying the type of depletion have already been presented.

Increases in Extracellular Sodium: Edema. The term edema as ordinarily employed refers merely to an increase in the volume of extracellular fluid. Although it is obvious that the administration of any fluid in excess of the body water needs and water excretory capacities, irrespective of its composition, will result in edema, most clinical instances of edema are etiologically related to a retention of sodium. If the increment is of sufficient magnitude, it may be clinically demonstrable by "pitting." Smaller changes are usually detectable only by serial measurements of the body weight. This definition by no means excludes the possibility of changes in cell water, nor does it include any statement about the concentration of serum sodium. Since we are concerned primarily with the vicissitudes of sodium and their effects, a detailed review of factors involved in the development of edema is beyond the scope of this presentation. It is germane to our discussion, however, to note that the term "cardiac" failure has been replaced by "congestive" failure, acknowledging thereby the importance of an excessively diminished renal plasma flow, decreased glomerular filtration rate and lowered sodium excretion in the genesis of edema.⁹⁴⁻¹⁰¹ Similarly, the ascites of cirrhosis should be ascribed to decreased sodium excretion influenced both by a rise in intra-abdominal pressure and by increased levels of antidiuretic substances rather than to consider it simply a manifestation of hypoproteinemia.¹⁰²⁻¹⁰⁸ In contrast to the complexity of factors operative in the genesis of edema the principles underlying therapy are quite uniform. Almost all instances of edema respond to sodium restriction; this may be facilitated by procedures which abstract sodium from the extracellular pool. Water restriction as a therapeutic procedure in edema is proba-

bly justifiable only in those clinical situations in which it is certain that the edema represents primarily a retention of water in excess of normal sodium stores. This particular combination is usually encountered in oliguric or anuric patients overtreated with glucose solutions during ill advised attempts to induce an elaboration of urine. In patients who are producing urine considerable attention may be profitably directed to mechanisms which facilitate the removal of sodium from extracellular fluid.

The ordinary "low salt diet" consisting of a variety of unseasoned foods cooked whenever possible in one or more changes of water still contains up to 2 gm. of sodium chloride equal to some 34 milliequivalents of sodium. In many edematous patients this degree of sodium restriction will induce a diuresis. Such a regimen, however, may prove inadequate; under such circumstances a dramatic response may be obtained by stringent restriction of sodium such as that possible with diets consisting of fruit juices and rice or of low sodium milk.¹⁰⁹⁻¹¹¹ Two liters of the low sodium milk prepared with distilled water and suitably fortified with lactose and sucrose will provide about 60 gm. of protein, 1,600 calories and only 2 milliequivalents of sodium per day. Patients have subsisted edema-free on this regimen for more than a year with serum albumin values as low as 0.36 gm. per cent.¹¹¹ It is to be noted that its effectiveness is not impaired by the considerable amounts of chloride administered, averaging 24 milliequivalents per day. The rice diet provides a comparably low sodium intake but differs in supplying only one-third as much protein. At times it may be advisable to combine a low-salt program with diuretics. This may be accomplished simply by administering large amounts of water in accordance with the program used by Schemm.¹¹² Other workers have pointed out, however, that this procedure is not always successful and that the beneficial effects reported are often more reasonably ascribable to other factors in the therapeutic program.^{113,114} It seems proba-

ble that forcing the fluid intake might prove successful in patients without impairment of renal water excretion, but it will certainly not succeed and even prove harmful in those incapable of increasing urinary losses of water.¹¹⁵ It has long been recognized that actual water intoxication may result.¹¹⁶⁻¹¹⁷ In view of these limitations the virtues of urea as a diuretic agent should not be disregarded. An oral intake of 30 or 40 gm. per day in patients in whom the blood non-protein nitrogen is normal will often prove highly effective. Of course if azotemia of moderate or high degree is already present, no such response will occur. If mercurial diuretics are used, it should be remembered that they can induce excessive losses of sodium and hence produce depletion of the normal body stores of this cation with the attendant circulatory risks described earlier.¹¹⁸⁻¹²¹ The adjuvant effects of acidifying salts should be kept in mind in employing the mercurial compounds.

Recently two new approaches to the therapy and control of edema have been tested. It has been reported that diuresis may be induced in edema by administering sodium salts and raising plasma tonicity.¹²²⁻¹²⁴ Also, cation exchange substances which either interfere with the absorption of sodium or which actually withdraw the electrolyte from body fluids as they are poured into the intestinal lumen have recently been tested.¹²⁵⁻¹³⁰ It is evident, however, that resins remove substances other than sodium, i.e., potassium, calcium, magnesium and even anions such as PO_4 . As a consequence undesirable and even dangerous depletions of body constituents may result. On the other hand, at this writing the carboxylic cation exchange resins appear to have less of these undesirable side effects although hypopotassemia has been observed.^{131,132}

Irrespective of the type or degree of sodium restriction or abstraction practiced the possibility of sodium depletion must be kept in mind since it can culminate in salt depletion shock and death. In addition to exercising reasonable clinical judgment in

modifying the stringency of the salt limitation once edema has disappeared precautions to be taken should include measurements of serum and urinary sodium levels. During intervals not characterized by delivery of edema fluid the urinary sodium in individuals with competent kidneys on a no-salt intake will fall off, as described earlier, almost to zero without hyponatremia. Another less specific clue to circulatory inadequacy following upon sodium depletion may be a rising blood non-protein nitrogen.

Sodium and Vascular Diseases. Clinical as well as experimental evidences in a variety of disease entities suggest that body sodium and the course of certain vascular diseases may be interrelated. It is generally acknowledged for example that the administration of saline solutions to patients with toxemia of pregnancy, eclampsia or acute glomerulonephritis may be followed with an exacerbation of signs and symptoms. Experimentally the hypertensive effects of DOCA are either dependent upon or can be accelerated by the simultaneous administration of sodium.¹³³⁻¹⁴¹ Moreover it has been reported that exacerbations in patients in a general hypertension clinic appeared to be related to the ratio of serum sodium to chloride.¹⁴² Finally the reported remissions in a wide assortment of patients with vascular disease maintained on a "rice diet" may be in part at least related to sodium restriction.^{110,143,144} The same observation has been made in a limited number of patients with vascular disease on an equally low sodium but higher protein milk diet.¹¹¹ At this point, in view of the contradictory reports,¹⁴⁵⁻¹⁴⁸ no final answer is available as to the relationships of sodium intake to the course of these various diseases. If it is true that these two variables are causally related, it is only fair to point out that these changes can also occur independently of one another. It may well be that sodium intake plays a role in the development or aggravation of those hypertensive manifestations associated with adrenal-cortical overactivity. This need not be the result, of

course, in frank clinical findings such as those encountered in Cushing's syndrome. Perhaps the resolution of these uncertainties will lie in continued attempts to separate the humoral and neurogenic factors in each specific instance of hypertensive disease in line with the studies of Perera.^{134, 137, 138} Some progress has also been made utilizing autonomic ganglion blocking agents such as tetraethylammonium chloride or bromide.¹⁴⁹⁻¹⁵² The final opinion must await further elucidation of facts. This may make it possible to define more clearly the role of sodium in vascular disease and point to the particular sequence of physiologic events following upon sodium administration or withdrawal. Another possibly important avenue of approach, essentially unexplored, is concerned with the significance of alterations in the cell sodium of the body.

Exchanges of and Changes in Cellular Sodium.

Under many circumstances it is useful to look upon changes in cell sodium and cell potassium as occurring reciprocally in terms of direction if not magnitude. This concept is not illogical in view of the preponderant extracellular position of sodium and the primarily cellular situation of potassium. Both cations, however, are found under normal physiologic circumstances in one another's domain. This is consistently true of potassium which is never completely excluded from the interstitial fluid and plasma; sodium on the other hand may be present in moderately high concentrations in certain tissues and be completely undetectable in others. This variability appears to be related to the characteristic composition of the various body tissues. Certain observations suggest, however, that in some disease states, insofar as cell sodium in aggregate is concerned, this moiety may increase beyond amounts characteristic of health.

It should be emphasized at the start that the calculations of the movement of cellular sodium are inferential.^{79, 153} The estimates which are obtained really represent only the non-extracellular balances of sodium. It is distinctly possible that the so-called

cellular sodium balance involves in part or even *in toto* the stores of sodium in bone or that the actual exchanges recorded, if of the lesser orders of magnitude, reflect errors in distinguishing between two large numbers. Speculation proves to be, however, far more fruitful if it is assumed that the non-extracellular sodium changes occur in tissues other than bone and that they are quantitatively real. Working within these premises a series of observations is available for interpretation. In a protracted sequence of recorded experimental studies changes in the water and the chief extracellular electrolyte are explicable only by postulating that cell base, whether sodium or potassium, may vary in amount as well as in osmotic effect.^{79, 154-158} Certain provocative discussions then become possible. Does such movement of sodium into and out of cells occur as a secondary or a primary process? In other words must potassium first be lost from cells as a result of dehydration, interruption of carbohydrate metabolism, etc.,¹ before sodium can move in? If this is so, this process represents merely an attempt to maintain cellular osmoticity even though the adjustment involves the entry of a cation whose intracellular concentrations are ordinarily low in health. An alternative consideration, however, has been suggested.¹⁵⁹ It is conceivable that the transfer of sodium into cells occurs as an initiating process with a secondary displacement of potassium into the extracellular compartment. Furthermore, if this alternative concept should indeed prove to represent the actual fact, it would simultaneously establish another factor productive of cell potassium deficits. Under such circumstances the cell potassium losses following upon, let us say, DOCA intoxication could be secondary to retention of sodium within cells. Irrespective of the final statement as to the actual sequence of events it is clear that under many but not all circumstances cell sodium and cell potassium seem to move in opposite directions. This has been demonstrated in diabetic acidosis and coma,^{160, 161} in renal failure,¹⁶² in subjects

with prolonged vomiting⁵⁹ and in those with diarrhea⁵² far in excess of values which could be ascribed to errors in calculating changes in the extracellular space and sodium therein.

However, changes in cell sodium have also been recorded without a reverse transfer of potassium and vice versa. This finding of course poses a further dilemma. If it is granted, as the data indicate, that the base within cells can change in amounts not matched by reciprocal alterations in another base, certain logical predications and deductions become permissible. First it is possible that such disparate movements can alter the total amount of osmotically active cell base. This change in turn might result in either (1) transfers of water between cells and interstitial fluid in response to osmotic forces or (2) inactivation or reactivation of cell constituents from the osmotic point of view. This latter possibility first raised several years ago¹⁵⁴⁻¹⁵⁸ necessitates some further elaboration. In those studies calculation of the total osmotically active cell base from the balances of extracellular water and of extracellular base concentrations yielded values which were at times greatly in excess of or greatly short of changes to be expected from the external balances of water sodium and potassium. Since these large differences fell outside the range of experimental error, activation and inactivation of cell base was postulated. Subsequent studies have confirmed this observation. At this time the factors which condition such changes and their significance are still not known. They may represent mechanisms (1) whereby base can be stored within cells without concomitant movement of water, (2) whereby the osmotically active cell base may be replenished from within the cell itself and (3) whereby cell water can be increased or decreased *without* movement of base into or out of cells. Various clinical situations can be postulated in which such processes might well be desirable from the point of view of maintaining body stores of base and water

relatively intact during physiologic processes in health and disease.

SUMMARY AND CONCLUSIONS

In view of the rapidly expanding data on body sodium it seems wise to emphasize the probably transient validity of this presentation. However, certain clear facts characterize our knowledge of extracellular sodium. Normally the kidneys, influenced in part by the steroids of the adrenal cortex as well as other hormones, adjust urinary excretions of this cation and of water to maintain constant both the concentration and total amount of sodium. Losses of sodium in considerable amounts in a short period of time produce circulatory collapse. Hypertonicity induced by relative or absolute deficits of water affects the nervous rather than the cardiovascular system and marked hypertonicity may cause respiratory failure. The use of sodium restriction, diuretics and of cation exchange resins in edematous patients has been discussed together with some mention of the role of sodium in vascular diseases. Several limitations in our knowledge of cell sodium have been noted, especially the inferential aspects of cell sodium data including transfer into and out of cells with or without reciprocal movements of potassium, the limitations in the accuracy of the sodium calculations, the absence of direct data in support of the concept of activation-inactivation of cell base and the lack of information concerning variations in the considerable bone depots of sodium.

REFERENCES

1. DANOWSKI, T. S. New concepts of the role of potassium in disease. *Am. J. Med.*, 7: 525, 1949.
2. HALD, P. M. Notes on the determination and distribution of sodium and potassium in cells and serum of normal human blood. *J. Biol. Chem.*, 163: 429, 1946.
3. NADAL, J. W., PEDERSEN, S. and MADDOCK, W. G. A comparison between dehydration from salt loss and from water deprivation. *J. Clin. Investigation*, 20: 691, 1941.
4. WINKLER, A. W., DANOWSKI, T. S., ELKINTON, J. R. and PETERS, J. P. Electrolyte and fluid studies during water deprivation and starvation in human subjects, and the effect of ingestion of fish,

- of carbohydrate, and of salt solutions. *J. Clin. Investigation*, 23: 807, 1944.
5. REASER, P. B. and BURCH, G. E. Radiosodium tracer studies in congestive heart failure. *Proc. Soc. Exper. Biol. & Med.*, 63: 543, 1946.
 6. HASTINGS, A. B. and COMPERE, E. L. Effect of bilateral suprarenalectomy on certain constituents of the blood of dogs. *Proc. Soc. Exper. Biol. & Med.*, 28: 376, 1931.
 7. LOEB, R. F. The adrenal cortex and electrolyte behavior. *Harvey Lect.*, p. 100, 1941-1942.
 8. FERREBEE, J. W., RAGON, C., ATCHLEY, D. W. and LOEB, R. F. Desoxycorticosterone esters. Certain effects in the treatment of Addison's disease. *J. A. M. A.*, 113: 1725, 1939.
 9. THORN, G. W., HOWARD, R. P. and EMERSON, K., JR. Treatment of Addison's disease with desoxycorticosterone acetate, a synthetic adrenal cortical hormone (preliminary report). *J. Clin. Investigation*, 18: 449, 1939.
 10. THORN, G. W., FORSHAM, P. H. and EMERSON, K. The Diagnosis and Treatment of Adrenal Insufficiency. Springfield, Ill., 1949. Charles C Thomas.
 11. LEAF, A., COUTER, W. T., LUTCHANSKY, M. and REIMER, A. Evidence that renal sodium excretion by normal human subjects is regulated by adrenal cortical activity. *J. Clin. Investigation*, 28: 1067, 1949.
 12. DORFMAN, R. I. Influence of adrenal cortical steroids and related compounds on sodium metabolism. *Proc. Soc. Exper. Biol. & Med.*, 72: 395, 1949.
 13. DEANE, H. W., SHAW, J. H. and GREEP, R. O. The effect of altered sodium or potassium intake on the width and cytochemistry of the zona glomerulosa of the rat's adrenal cortex. *Endocrinology*, 43: 133, 1948.
 14. BADINEZ, O. and CROXATTO, H. Histological changes in the adrenal cortex of the rat caused by administration of potassium chloride or sodium chloride. *Bol. Soc. biol. Santiago, Chile*, 5: 40, 1948.
 15. DEANE, H. W. The control of the secretory activity of the zona glomerulosa of the adrenal cortex in the rat, as revealed by cytochemical observations. *Am. A. Advancement Sc.*, Sixth New York Meeting, p. 232, 1949.
 16. JONES, I. C. The relationship of the mouse adrenal cortex to the pituitary. *Endocrinology*, 45: 514, 1949.
 17. ENGSTROM, W. W. Nature and significance of neutral steroids in human urine in normal and in abnormal states. *Yale J. Biol. & Med.*, 21: 21, 1948.
 18. GRIGGS, D. E. and JOHNS, V. J. Influence of mercurial diuretics on the excretion of sodium, potassium, and chlorides. *California Med.*, 69: 133, 1948.
 19. RYTAND, D. A. and CRISMON, J. M. Excretion rhythms of water and electrolytes in the nephrotic syndrome. *J. Clin. Investigation*, 27: 554, 1948.
 20. GAUNT, R., BIRNIE, J. H. and EVERSOLE, W. J. Adrenal cortex and water metabolism. *Physiol. Rev.*, 29: 281, 1949.
 21. THORN, G. W., BAYLES, R. B., MASSELL, B. F., FORSHAM, P. H., HILL, S. R., JR., SMITH, III, S. T. and WARREN, J. E. Medical progress: studies on the relation of pituitary-adrenal function to rheumatic disease. *New England J. Med.*, 241: 529, 1949.
 22. JACOBSEN, A. W., KOEFF, G. F., TALBOT, N. B. and WILKINS, L. The adrenal gland in health and disease. *Pediatrics*, 3: 515, 1949.
 23. Editorial. Some aspects of adrenal cortical function and pituitary-adrenal relationships. *Ann. Int. Med.*, 31: 925, 1949.
 24. FORSHAM, P. H., THORN, G. W., PRUNTY, F. T. G. and HILLS, A. G. Clinical studies with pituitary adrenocorticotropin. *J. Clin. Endocrinol.*, 8: 15, 1948.
 25. MASON, H. L., POWER, M. H., RYNEARSON, E. H., CIORAMELLI, L. C., LI, C. H. and EVANS, H. M. Results of administration of anterior pituitary adrenocorticotrophic hormone to a normal human subject. *J. Clin. Endocrinol.*, 8: 1, 1948.
 26. LEITER, L. The role of sodium chloride in the mechanism and treatment of congestive heart failure. *Bull. New York Acad. Med.*, 24: 702, 1948.
 27. SARTORIUS, O. W. and ROBERTS, K. The effects of pitressin and desoxycorticosterone in low dosage on the excretion of sodium, potassium, and water by the normal dog. *Endocrinology*, 45: 273, 1949.
 28. MEANS, J. H. The Thyroid and Its Disease, 2nd ed. Philadelphia, 1948. J. B. Lippincott Co.
 29. THORN, G. W., NELSON, K. R. and THORN, D. W. A study of the mechanism of edema associated with menstruation. *Endocrinology*, 22: 155, 1938.
 30. THORN, G. W. and EMERSON, K., JR. The role of gonadal and adrenal cortical hormones in the production of edema. *Ann. Int. Med.*, 14: 757, 1940.
 31. STIEGLITZ, E. J. and KIMBLE, S. T. Premenstrual intoxication. *Am. J. M. Sc.*, 218: 616, 1949.
 32. GAMBLE, J. L., ROSS, S. G. and TISDALL, F. F. Metabolism of fixed base during fasting. *J. Biol. Chem.*, 57: 633, 1923.
 33. McCANCE, R. A. The excretion of urea, salts and water during periods of hydropaenia in man. *J. Physiol.*, 104: 196, 1945.
 34. McCANCE, R. A. Medical problems in mineral metabolism. I. Legacies of evolution. *Lancet*, 230: 643, 1936.
 35. NADAL, J. W. Diagnosis of dehydration in surgical conditions. *Am. J. Surg.*, 56: 282, 1942.
 36. MARRIOTT, H. L. Water and salt depletion. *Brit. M. J.*, 1: 245, 1947.
 37. MARRIOTT, H. L. Water and salt depletion. *Brit. M. J.*, 1: 285, 1947.
 38. MARRIOTT, H. L. Water and salt depletion. *Brit. M. J.*, 1: 328, 1947.
 39. McCANCE, R. A. and WIDDOWSON, E. M. The secretion of urine in man during experimental salt deficiency. *J. Physiol.*, 91: 222, 1937.
 40. MARRIOTT, H. L. Water and Salt Depletion. Springfield, Ill., 1950. Charles C Thomas.
 41. BRODIE, B. B., FRIEDMAN, M. M. and FERRARO, L. R. Studies on extracellular fluid. *J. Biol. Chem.*, 140: Proc. 11, 1941.
 42. KALTREIDER, N. L., MENEELY, G. R., ALLEN, J. R. and BALE, W. F. Determination of the volume

- of the extracellular fluid of the body with radioactive sodium. *J. Exper. Med.*, 74: 569, 1941.
43. MOORE, F. D. Determination of total body water and solids with isotopes. *Science*, 104: 157, 1946.
 44. ELKINTON, J. R. The volume of distribution of mannitol as a measure of the volume of extracellular fluid, with a study of the mannitol method. *J. Clin. Investigation*, 26: 1088, 1947.
 45. SCHECHTER, A. J., CORY, M. K., CARPENTIER, A. L. and DARROW, D. C. Changes in the composition of fluids injected into the peritoneal cavity. *Am. J. Dis. Child.*, 46: 1015, 1933.
 46. HARRISON, H. E., DARROW, D. C. and YANNET, H. The total electrolyte content of animals and its probable relation to the distribution of body water. *J. Biol. Chem.*, 113: 515, 1936.
 47. ELKINTON, J. R., DANOWSKI, T. S. and WINKLER, A. W. Hemodynamic changes in salt depletion and in dehydration. *J. Clin. Investigation*, 25: 120, 1946.
 48. DANOWSKI, T. S., WINKLER, A. W. and ELKINTON, J. R. The treatment of shock due to salt depletion: comparison of the hemodynamic effects of isotonic saline, of hypertonic saline, and of isotonic glucose solutions. *J. Clin. Investigation*, 25: 130, 1946.
 49. ELKINTON, J. R., WINKLER, A. W. and DANOWSKI, T. S. The importance of volume and of tonicity of the body fluids in salt depletion shock. *J. Clin. Investigation*, 26: 1002, 1947.
 50. McCANCE, R. A. Medical problems in mineral metabolism. II. Sodium deficiencies in clinical medicine. *Lancet*, 230: 704, 1936.
 51. DANOWSKI, T. S., WINKLER, A. W. and PETERS, J. P. Salt depletion, peripheral vascular collapse, and the treatment of diabetic acidosis. *Yale J. Biol. & Med.*, 18: 405, 1946.
 52. DARROW, D. C. The retention of electrolyte during recovery from severe dehydration due to diarrhea. *J. Pediat.*, 28: 515, 1946.
 53. FLETT, J., JR., PRATT, E. L. and DARROW, D. C. Treatment of diarrhea with potassium and sodium salts. *Am. J. Dis. Child.*, 77: 105, 1949.
 54. DARROW, D. C., PRATT, E. L., FLETT, J., JR., GAMBLE, A. H. and WIESE, H. F. Disturbances of water and electrolytes in infantile diarrhea. *Pediatrics*, 3: 129, 1949.
 55. GAMBLE, J. L. Deficits in diarrhea. *J. Pediat.*, 30: 488, 1947.
 56. HARTWELL, J. A. and HOGUET, J. P. Experimental intestinal obstruction in dogs with especial reference to the cause of death and the treatment by large amounts of normal saline solution. *J. A. M. A.*, 59: 82, 1912.
 57. McVICAR, C. S. A discussion of the clinical and laboratory clinical findings in certain cases of obstruction in the upper gastrointestinal tract. The role of blood chemistry in diagnosis, prognosis and treatment of this condition. *Am. J. M. Sc.*, 169: 224, 1925.
 58. GAMBLE, J. L. and McIVER, M. A. Body fluid changes due to continued loss of the external secretion of the pancreas. *J. Exper. Med.*, 48: 859, 1928.
 59. DANOWSKI, T. S., AUSTIN, A. C., GOW, R. C., MATEER, F. M., WEIGAND, F. A., PETERS, J. H. and GREENMAN, L. Electrolyte and nitrogen balance studies in infants following cessation of vomiting. *Pediatrics*, 5: 57, 1950.
 60. ROSENTHAL, S. M. Experimental chemotherapy of burns and shock. iv. Production of traumatic shock in mice. v. Therapy with mouse serum and sodium salts. *Pub. Health Rep.*, 58: 1429, 1943.
 61. DARROW, D. C. The importance of deficit of sodium and chloride in dehydration. *J. Pediat.*, 13: 670, 1938.
 62. FOX, C. L., JR. Oral sodium lactate in the treatment of burn shock. *J. A. M. A.*, 124: 207, 1944.
 63. HARROP, G. A., NICKOLSON, W. M., SOFFER, L. J. and STRAUSS, M. Extracellular and intracellular water loss during suprarenal insufficiency in the dog. *Proc. Soc. Exper. Biol. & Med.*, 32: 1312, 1935.
 64. SWINGLE, W. W. and REMINGTON, J. W. The role of the adrenal cortex in physiological processes. *Physiol. Rev.*, 24: 89, 1944.
 65. CLARKE, A. P. W., CLEGHORN, R. A., FERGUSON, J. K. W. and FOWLER, J. L. A. Factors concerned in the circulatory failure of adrenal insufficiency. *J. Clin. Investigation*, 26: 359, 1947.
 66. JAUDON, J. C. Hypofunction of the adrenals in early life. *J. Pediat.*, 29: 696, 1946.
 67. JAUDON, J. C. Further observations concerning hypofunction of the adrenals during early life., "Salt and water" hormone deficiency. *J. Pediat.*, 32: 641, 1948.
 68. THORN, G. W., KOEPF, G. F. and CLINTON, M., JR. Renal failure simulating adrenocortical insufficiency. *New England J. Med.*, 231: 76, 1944.
 69. SAWYER, W. H. and SOLEZ, C. Salt-losing nephritis simulating adrenocortical insufficiency. *New England J. Med.*, 240: 210, 1949.
 70. BORST, J. R. Disturbances in water and salt metabolism in the final stage of chronic renal insufficiency. *Acta med. Scandinav.*, 136: 1, 1949.
 71. DANOWSKI, T. S., WINKLER, A. W. and ELKINTON, J. R. Biochemical and hemodynamic changes following the subcutaneous injection of glucose solution. *J. Clin. Investigation*, 26: 887, 1947.
 72. WINKLER, A. W., DANOWSKI, T. S. and ELKINTON, J. R. The role of colloid and of saline in the treatment of shock. *J. Clin. Investigation*, 25: 220, 1946.
 73. KERPEL-FRONIUS, E. Ueber die Beziehungen zwischen Salz und Wasserhaushalt bei experimentellen Wasserhaushalt. *Ztschr. f. Kinderh.*, 57: 489, 1935.
 74. KERPEL-FRONIUS, E. Durstexsikkose and Salzmengelextsikkose. *Acta paediat.*, 22: 143, 1937.
 75. RAPOPORT, S. Hyperosmolarity and hyperelectrolytemia in pathologic conditions of childhood. *Am. J. Dis. Child.*, 74: 682, 1947.
 76. BROCH, O. J. Premortal changes in the concentration of the serum electrolytes. *Acta med. Scandinav.*, 131: 1, 1948.
 77. KERPEL-FRONIUS, E. Dehydration by deprivation of fluids. *Paediat. danub.*, 1: 33, 1947.
 78. WINKLER, A. W., ELKINTON, J. R., HOPPER, J., JR. and HOFF, H. E. Experimental hypertonicity: alterations in the distribution of body water and the cause of death. *J. Clin. Investigation*, 23: 103, 1944.

79. ELKINTON, J. R., WINKLER, A. W. and DANOWSKI, T. S. Transfers of cell sodium and potassium in experimental and clinical conditions. *J. Clin. Investigation*, 27: 74, 1948.
80. BLACK, D. A. K., McCANCE, R. A. and YOUNG, W. F. A study of dehydration by means of balance experiments. *J. Physiol.*, 102: 406, 1944.
81. ELKINTON, J. R. and WINKLER, A. W. Physiological effects of drinking undiluted sea water. *War Med.*, 6: 241, 1944.
82. NEWBURGH, L. H. The foundations of diet therapy. *J. A. M. A.*, 105: 1034, 1935.
83. McCANCE, R. A. and YOUNG, W. F. The secretion of urine during dehydration and rehydration. *J. Physiol.*, 102: 415, 1944.
84. GAMBLE, J. L. and BUTLER, A. M. Measurement of the renal water requirement. *Tr. A. Am. Physicians*, 58: 157, 1944.
85. McCANCE, R. A. and YOUNG, W. F. Observations on water metabolism. *Brit. M. Bull.*, 2: 219, 1944.
86. COLLIER, F. A., IOB, V., VAUGHAN, H. H., KALDER, N. B. and MOYER, C. A. Translocation of fluid produced by the intravenous administration of isotonic salt solutions in man postoperatively. *Ann. Surg.*, 122: 663, 1945.
87. BUTLER, A. M. and TALBOT, N. B. Parenteral-fluid therapy. i. Estimation and provision of daily maintenance requirements. *New England J. Med.*, 231: 585, 1944.
88. BUTLER, A. M. and TALBOT, N. B. Parenteral-fluid therapy. ii. The estimation of losses incident to starvation and dehydration with acidosis or alkalosis and the provision of repair therapy. *New England J. Med.*, 231: 621, 1944.
89. YOUNG, W. F., HALLUM, J. L. and McCANCE, R. A. The secretion of urine by premature infants. *Arch. Dis. Childhood*, 16: 243, 1941.
90. McCANCE, R. A. and YOUNG, W. F. The secretion of urine by newborn infants. *J. Physiol.*, 99: 265, 1941.
91. McCANCE, R. A. Renal function in early life. *Physiol. Rev.*, 28: 331, 1948.
92. RUBIN, M. I., BRUCK, E. and RAPOPORT, M. Maturation of renal function in childhood: clearance studies. *J. Clin. Investigation*, 28: 1144, 1949.
93. BARNETT, H. L. Kidney function in young infants. *Pediatrics*, 5: 171, 1950.
94. FUTCHER, P. H. and SCHROEDER, H. A. Studies on congestive heart failure. ii. Impaired renal excretion of sodium chloride. *Am. J. M. Sc.*, 204: 52, 1942.
95. TURNER, H., JAMES, D. F. and MERRILL, A. J. Studies on the mechanism of reduction in renal flow in heart failure. Preliminary report. *Am. J. Med.*, 5: 619, 1948.
96. MOKOTOFF, R., ROSS, G. and LEITER, L. Renal plasma flow and sodium reabsorption and excretion in congestive heart failure. *J. Clin. Investigation*, 27: 1, 1948.
97. BURCH, G. E., THREEFOOT, S. A. and REASER, P. B. Some aspects of renal excretion of Na^{24} by normal subjects and by patients with congestive heart failure. *Stanford M. Bull.*, 6: 81, 1948.
98. STEAD, E. A., JR. Edema of heart failure. *Bull. New York Acad. Med.*, 24: 607, 1948.
99. STARR, I. Our changing viewpoint about congestive failure. *Ann. Int. Med.*, 30: 1, 1949.
100. MERRILL, A. J. Mechanisms of salt and water retention in heart failure. *Am. J. Med.*, 6: 357, 1949.
101. WESSON, L. G., ANSLOW, W. P., JR. and SMITH, H. W. The excretion of strong electrolytes. *Bull. New York Acad. Med.*, 24: 586, 1948.
102. LAYNE, J. A. and SCHEMM, F. R. The use of high fluid intake and low-sodium acid-ash diet in management of portal cirrhosis with ascites. *Gastroenterology*, 9: 705, 1947.
103. McKEE, F. W., SCHLOERB, P. R., SCHILLING, J. A., TISHKOFF, G. H. and WHIPPLE, G. H. Protein metabolism and exchange as influenced by constriction of the vena cava. Experimental ascites an internal plasmapheresis: sodium chloride and protein intake predominant factors. *J. Exper. Med.*, 87: 457, 1948.
104. FALoon, W. W., ECKHARDT, R. D., COOPER, A. N. and DAVIDSON, C. S. Changes in sodium excretion in patients with cirrhosis of the liver following intravenous administration of albumin, mercurial diuretics and a low sodium diet. *Am. J. Med.*, 5: 623, 1948.
105. BRADLEY, S. E., MUDGE, G. H., BLAKE, W. D. and ALPHONSE, P. The effect of increased intra-abdominal pressure upon renal excretion of water, sodium and potassium in normal human subjects and in patients with diabetes insipidus. *J. Clin. Investigation*, 28: 772, 1949.
106. LESLIE, S., STUECK, G. H., JR., SHORR, H. M. and RALLI, E. P. Chemical and physiological changes during water tolerance tests in patients with cirrhosis. *Federation Proc.*, 7: 71, 1948.
107. FALoon, W. W., ECKHARDT, R. D., COOPER, A. M. and DAVIDSON, C. S. The effect of human serum albumin, mercurial diuretics, and a low sodium diet on sodium excretion in patients with cirrhosis of the liver. *J. Clin. Investigation*, 28: 595, 1949.
108. FARNSWORTH, E. B. and KRAKUSIN, J. S. Electrolyte partition in patients with edema of various origins. Qualitative and quantitative definition of cations and anions in hepatic cirrhosis. *J. Lab. & Clin. Med.*, 33: 1545, 1948.
109. KEMPNER, W. Some effects of the rice diet treatment of kidney disease and hypertension. *Bull. New York Acad. Med.*, 22: 358, 1946.
110. KEMPNER, W. Treatment of hypertensive vascular disease with rice diet. *Am. J. Med.*, 4: 545, 1948.
111. GREENMAN, L., PETERS, J. H., MATEER, F. and DANOWSKI, T. S. Unpublished data.
112. SCHEMM, F. R. Certain clinical aspects of the application of water balance principles to heart and kidney disease. *Ann. Int. Med.*, 30: 92, 1949.
113. BRIDGES, W. C., WHEELER, E. O. and WHITE, P. D. Low-sodium diet and free fluid intake in the treatment of congestive heart failure. *New England J. Med.*, 234: 573, 1946.
114. NEWMAN, A. A. and STEWARD, H. J. Experience with the Schemm regimen in the treatment of congestive heart failure. *Ann. Int. Med.*, 28: 916, 1948.

115. GOETTSCH, E., LIPPMAN, R. W. and LUETSCHER, J. A., JR. Certain electrolyte disturbances in renal insufficiency. *Pediatrics*, 5: 147, 1950.
116. WEIR, J. F., LARSON, E. E. and ROWNTREE, L. G. Studies in diabetes insipidus, water balance and water intoxication. *Arch. Int. Med.*, 29: 306, 1922.
117. HELWIG, F. C., SCHUTZ, C. B. and CURRY, D. E. Water intoxication. Report of a fatal human case, with clinical, pathologic and experimental studies. *J. A. M. A.*, 104: 1569, 1935.
118. WHEELER, E. O., BRIDGES, W. C. and WHITE, P. D. Diet low in salt (sodium) in congestive heart failure. *J. A. M. A.*, 133: 16, 1947.
119. MACGUIRE, W. B., JR. Risk of uremia due to sodium depletion. *J. A. M. A.*, 137: 1377, 1948.
120. SCHROEDER, H. A. Renal failure associated with low extracellular sodium chloride. The low salt syndrome. *J. A. M. A.*, 141: 117, 1949.
121. SOLOFF, L. A. and ZATUCHNI, J. Syndrome of salt depletion. Induced by a regimen of sodium restriction and sodium diuresis. *J. A. M. A.*, 139: 1136, 1949.
122. FOX, C. L., JR. and McCUNE, D. J. Electrolyte changes in nephrosis. *Am. J. M. Sc.*, 216: 1, 1948.
123. FOX, C. L., JR. and McCUNE, D. J. Electrolyte studies in nephrosis: induction of diuresis by administration of salts of sodium and potassium. *Am. J. Dis. Child.*, 77: 102, 1949.
124. FOX, C. L., JR. Significance of electrolyte abnormalities in management of anuria, oliguria and edema. *Am. J. Med.*, 7: 417, 1949.
125. DOCK, W. Sodium depletion as a therapeutic procedure: the value of ion-exchange resins in withdrawing sodium from the body. *Tr. A. Am. Physicians*, 59: 282, 1946.
126. GORDON, G. B., WEITZNER, H. A. and BARNARD, R. D. Removal of sodium from biologic menstrooms by calcium zeolites. *Ohio J. Sc.*, 48: 65, 1948.
127. CRISMON, J. M. Sodium and potassium depletion in rats by means of cation exchange resins mixed with food. *Federation Proc.*, 8: 30, 1949.
128. IRWIN, L., BERGER, E. Y., ROSENBERG, B. and JACKENTHAL, R. The effect of a cation exchange resin on electrolyte balance and its use in edematous states. *J. Clin. Investigation*, 28: 1403, 1949.
129. CHEN, J. S. and FREEMAN, S. The removal of cations from solutions and the rat's alimentary canal by H-form resins. *J. Lab. & Clin. Med.*, 35: 99, 1950.
130. MCCHESENEY, E. W. and MCAULIFF, J. P. Effects of some ion exchange resins on mineral metabolism of rats. *Am. J. Physiol.*, 160: 264, 1950.
131. ELKINTON, J. R. Personal communication.
132. DANOWSKI, T. S., GREENMAN, L., MATEER, F., PETERS, J. H., WEIGAND, F. A., MERMELSTEIN, H. and CLARKE, C. E. Carboxylic cation exchange resin studies in animals and humans. *J. Clin. Investigation*, 29: 807, 1950.
133. SELYE, H., HALL, C. E. and ROWLEY, E. M. Malignant hypertension produced by treatment with desoxycorticosterone acetate and sodium chloride. *Canad. M. A. J.*, 49: 88, 1943.
134. PERERA, G. A. The relationship of the adrenal cortex to hypertension. *J. A. M. A.*, 129: 537, 1945.
135. HALL, C. E., DONTIGNY, P., BELAND, E. and SELYE, H. The role of the adrenals in the production of nephrosclerosis by anterior pituitary preparations. *Endocrinology*, 38: 296, 1946.
136. KNOWLTON, A. I., LOEB, E. N., STOERK, H. C. and SEEGAL, B. C. Desoxycorticosterone acetate. The potentiation of its activity by sodium chloride. *J. Exper. Med.*, 85: 187, 1947.
137. PERERA, G. A. and BLOOD, D. W. Pressor activity of desoxycorticosterone acetate in normotensive and hypertensive subjects. *Ann. Int. Med.*, 27: 401, 1947.
138. PERERA, G. A. and BLOOD, D. W. The relationship of sodium chloride to hypertension. *J. Clin. Investigation*, 26: 1109, 1947.
139. GREEN, D. M., COLEMAN, D. H. and McCABE, M. Mechanisms of desoxycorticosterone action. II. Relation of sodium chloride intake to fluid exchange, pressor effects and survival. *Am. J. Physiol.*, 154: 465, 1948.
140. FRIEDMAN, S. M., FRIEDMAN, C. L. and POLLEY, J. R. Potentiation of the hypertensive effects of desoxycorticosterone acetate (DOCA) by various sodium salts. *Am. J. Physiol.*, 153: 226, 1948.
141. GREEN, D. M. Mechanisms of desoxycorticosterone action. I. Relation of fluid intake to blood pressure. *J. Lab. & Clin. Med.*, 33: 853, 1948.
142. SELYE, F. L. Biochemical changes in hypertension. *Canad. M. A. J.*, 57: 325, 1947.
143. BRYANT, J. M. and BLECHA, E. Low sodium-forced fluid management of hypertensive vascular disease and hypertensive heart disease. *Proc. Soc. Exper. Biol. & Med.*, 65: 227, 1947.
144. CONTRATTO, A. W. and ROGERS, M. B. The use of the rice diet in the treatment of hypertension in nonhospitalized patients. *New England J. Med.*, 239: 531, 1948.
145. SCHROEDER, H. A. Low salt diets and arterial hypertension. *Am. J. Med.*, 4: 578, 1948.
146. LANDOWNE, M., THOMPSON, W. and RUBY, B. Minimal sodium diet; a controlled study on its effect upon the blood pressure of ambulatory hypertensive subjects. *Am. J. Med.*, 6: 664, 1949.
147. ROSENBERG, B., ROSENTHAL, A. E. and ROSENBLUTH, M. B. Effect of the low sodium diet and the rice diet on arterial blood pressure. *Am. J. Med.*, 5: 815, 1948.
148. CHASIS, H., GOLDRING, W., BREED, E., BOLOMEY, A. and SMITH, H. W. Effects of salt and protein restriction on blood pressure and renal hemodynamics in hypertensive patients. *J. Clin. Investigation*, 28: 775, 1949.
149. BJORCK, G. and EJRP, B. Experiences with tetraethylammoniumbromide. *Acta med. scandinav.*, 133: 299, 1949.
150. LADUE, J. S., MURISON, P. J. and PACK, G. T. The use of tetraethylammonium bromide as a diagnostic test for pheochromocytoma. *Ann. Int. Med.*, 29: 914, 1948.
151. BRUST, A. A., ASSALI, N. S. and FERRIS, E. B. Evaluation of neurogenic and humoral factors in blood pressure maintenance in normal and toxemic pregnancy using tetraethylammonium chloride. *J. Clin. Investigation*, 27: 717, 1948.

152. STEAD, W. W., REISER, M. F., RAPOPORT, S. and FERRIS, E. B. The effect of sodium chloride depletion on blood pressure and tetraethylammonium chloride response in hypertension. *J. Clin. Investigation*, 27: 766, 1948.
153. ELKINTON, J. R. and TAFFEL, M. Prolonged water deprivation in the dog. *J. Clin. Investigation*, 21: 787, 1942.
154. ELKINTON, J. R., WINKLER, A. W. and DANOWSKI, T. S. Inactive cell base and the measurement of changes in cell water. *Yale J. Biol. & Med.*, 17: 383, 1944.
155. MILLER, H. C. and DARROW, D. C. Relation of muscle electrolyte to alterations in serum potassium and to the toxic effects of injected potassium chloride. *Am. J. Physiol.*, 130: 747, 1940.
156. YANNET, H. and DARROW, D. C. The effect of depletion of extracellular electrolytes on the chemical composition of skeletal muscle, liver, and cardiac muscle. *J. Biol. Chem.*, 134: 721, 1940.
157. CONWAY, E. J. and HINGERTY, D. Relations between potassium and sodium levels in mammalian muscle and blood plasma. *Biochem. J.*, 42: 372, 1948.
158. DARROW, D. C. Body fluid physiology: the relation of tissue composition to problems of water and electrolyte balance. *New England J. Med.*, 233: 91, 1945.
159. ELKINTON, J. R. Personal communication of unpublished data.
160. DANOWSKI, T. S., PETERS, J. H., RATHBUN, J. C., QUASHNOCK, J. M. and GREENMAN, L. Studies in diabetic acidosis and coma, with particular emphasis on the retention of administered potassium. *J. Clin. Investigation*, 28: 1, 1949.
161. GREENMAN, L., MATEER, F. M., GOW, R. C., PETERS, J. H. and DANOWSKI, T. S. Some observations on the development of hypokalemia during therapy of diabetic acidosis in juvenile and young adult subjects. *J. Clin. Investigation*, 28: 409, 1949.
162. ELKINTON, J. R., TARAIL, R. and PETERS, J. P. Transfers of potassium in renal insufficiency. *J. Clin. Investigation*, 28: 378, 1949.

Seminars on Pulmonary Physiology

Physiopathologic Aspects of Chronic Pulmonary Emphysema*

JOHN R. WEST,† M.D., ELEANOR DEF. BALDWIN,‡ M.D.,
ANDRÉ Cournand, M.D. and DICKINSON W. RICHARDS, JR., M.D.

New York, New York

It has long been recognized that chronic pulmonary emphysema is of common occurrence not only as a primary disorder of the lungs or as a late result of long-standing bronchial disease but also as a complication of other major pulmonary diseases, particularly silicosis and other fibroses. Only in recent years, however, have attempts been made to define the essential physiologic disturbances which result from emphysema. A physiologic evaluation is a necessary one, for the pathologic findings are extremely variable and do not necessarily indicate the severity of the disease insofar as clinical manifestations are concerned. Thus small localized blebs on the surface of the lung must undoubtedly be classed as emphysema but are obviously of no clinical importance *per se* unless, by rupture, one leads to spontaneous pneumothorax. A great proportion of large air cysts are also forms of emphysema, the clinical significance of which are not always apparent on pathologic examination. Finally, there is no consistent relationship between the clinical severity of diffuse bilateral pulmonary emphysema and the extent of the process seen at necropsy.

Accordingly, there will be presented in this paper an integrated concept of the physiologic disturbances which result from chronic diffuse pulmonary emphysema from the standpoint of alterations produced in lung volumes, mechanics of breathing, the distribution of air and blood in the lungs and gas exchange. The relationship of these disturbances to the pathology of the disease will be considered as will the mechanisms by which these alterations result in the clinical

manifestations of the disease. Finally, a physiologic classification previously described¹ will be discussed; individual cases will be presented to illustrate this classification and the principles of therapy will be summarized briefly.

No attempt will be made to review the literature pertaining to this subject except insofar as the work relates to the concept of pulmonary function here described. But the studies of many investigators are germane to this subject, e.g., Loeschcke² and Christie³ emphasized the importance of chest deformity and loss of pulmonary elasticity, respectively, as mechanical factors in the development of pulmonary insufficiency in emphysema. Knipping et al.,^{4,5} using the relatively simple technic of spirometry, postulated the importance of inadequate ventilation during activity as well as imbalance between alveolar ventilation and perfusion as causes of arterial anoxia. The latter hypothesis was supported by observations on the intrapulmonary mixing of gases which have indicated by a variety of methods in the hands of several investigators⁶⁻¹⁰ that ventilation of the emphysematous lung is characteristically not uniform throughout. The importance of lung volume measurements, especially the ratio of residual volume to total lung capacity, as indices of the severity of the disease was emphasized by Hurtado.^{11,12} Kaltreider and McCann¹³ called attention to the usefulness of physical exercise in accentuating disturbances in lung function which might be masked at rest.

Baldwin, Cournand and Richards¹ made detailed observations on a large number of patients

* From the Department of Medicine, Columbia University College of Physicians and Surgeons, and the Cardio-Pulmonary Laboratories of the Presbyterian Hospital and of the First Medical and Chest Services (Columbia University Division), Bellevue Hospital, New York, N. Y. This work was supported by grants from the Commonwealth Fund and the Life Insurance Medical Research Fund.

† Life Insurance Medical Research Fellow.

‡ Dr. Baldwin died on January 16, 1951.

with chronic pulmonary emphysema and offered a functional classification of the disease based upon the presence or absence of significant arterial anoxia and hypercapnia after exercise and the presence or absence of clinical involvement of the heart by the disease. These authors emphasized the importance of local alveolar ventilation-perfusion imbalance in the production of arterial anoxia and hypercapnia, but it was not until the development of appropriate techniques by Riley et al.¹⁴⁻¹⁷ that the extent of this imbalance as well as the oxygen diffusing capacity of the lungs could be estimated.

PHYSIOLOGIC MEASUREMENTS AND THEIR RELATIONSHIP TO ANATOMIC AND CLINICAL FINDINGS

Lung Volumes. Among the characteristic findings in chronic pulmonary emphysema are alterations in the total lung capacity, residual volume and vital capacity. These changes are noteworthy for two reasons. In the first place, they are of considerable diagnostic importance; secondly, certain pathologic changes which have important effects upon the function of the lungs are reflected in these alterations in lung volumes.

The lungs of the patient with chronic pulmonary emphysema are in a state of chronic hyperinflation which is usually quite obvious on physical and x-ray examination. As a result of this chronic hyperinflation the total lung volume may become larger than normal, but more striking is the increase in the ratio of the residual volume to the total lung capacity, a reflection of the characteristic inability to empty the lungs to a normal extent upon forced expiration. The vital capacity will of course depend upon the size of the residual volume and total lung capacity and may be greatly affected or not affected at all.

The alterations are the result of the interplay of several factors. One of the chief pathologic features of pulmonary emphysema is a loss or fragmentation of pulmonary elastic tissue. Since the normal resting position of the chest (the position at the end of a quiet expiration) is the result of a state of equilibrium reached between elastic forces in the lungs which tend to reduce the volume and elastic forces in the chest wall which tend to increase the volume of the chest, it follows that reduction in the elastic forces within the lung itself will result in a shift of the resting position toward the inspiratory position, i.e., the position of hyperinflation.

In addition to reduction in pulmonary elas-

ticity pulmonary emphysema is characterized by a variable degree of more or less widespread bronchiolar narrowing, a result of accumulated secretions, mural thickening, mucosal edema and bronchospasm. In consequence, accentuation of the tendency to hyperinflation occurs because in this position the bronchioles are widened as much as they can be; and since the patient's pulmonary ventilation is thus carried on with least obstruction, the inspiratory chest position is naturally assumed and maintained.

Although an elevation of the ratio of residual volume to total lung capacity is of such frequent occurrence in emphysema that the diagnosis should not be made in its absence, there is only a fair correlation between this ratio and the clinical severity of the disease for two main reasons. In the first place, alterations in lung volumes are the result largely of bronchial and elastic tissue factors which are only part of the whole picture. Secondly, as the disease progresses in severity the presence of blebs, bullae and air cysts becomes more prominent. Many of these communicate poorly or not at all with the tracheobronchial tree and as a result are inaccessible to physiologic measurement. Thus in some instances an obviously hyperinflated chest with a tremendous volume on physical or roentgen examination will be found to have a reduced total lung capacity by physiologic measurement. For this reason the measured lung volumes may have a physiologic rather than an anatomic meaning in the more advanced stages of the disease. Furthermore, these changes in lung volumes are at best only static measurements which require considerable interpretation before their significance with respect to deranged lung function is clear.

Definitely more important in any consideration of the effect of pulmonary emphysema upon pulmonary function are the changes wrought by this disease in the mechanics of breathing.

Mechanics of Breathing. That emphysema grossly disturbs the mechanics of the chest below is usually readily apparent on examination of the patient. The severity of the disturbance is of course quite variable from patient to patient but there is a pattern of dysfunction common to most. There is, in the first place, a reduction in the normally predominant diaphragmatic and lower costal action in ventilation and an increased utilization of the upper costal portion of the chest and the accessory muscles of respiration. In some instances the lower ribs are actually retracted at

the beginning of inspiration by the contraction of the diaphragm. As a rule the entire chest cage is lifted upward as a unit on inspiration by means of strong contractions of the accessory muscles. Incoordination of the muscles of respiration is not uncommon,¹⁸ accessory muscles sometimes remaining contracted even after expiration has begun. The extremely important factor of bronchiolar narrowing is manifest by sibilant and sonorous rhonchi, expiratory prolongation and other signs of obstructed breathing.

Through use of the recording spirometer these changes are easily brought out. The spirogram in obstructive emphysema is quite characteristic. (Fig. 1.) The features to be noted are incoordination of respiratory movement, expiratory prolongation, air trapping on successive deep breaths and execution of the maximum breathing capacity in the extreme inspiratory position. Maximum breathing capacity is markedly reduced as a rule.

These alterations in the function of the chest bellows are directly attributable to the pathologic changes of emphysema. Bronchiolar obstruction, by increasing the viscous and turbulent resistance to air movement in the respiratory passages, greatly increases the amount of work required in breathing. Reduction in lung elasticity results in insufficient storage of elastic energy during inspiration to meet the needs of expiration; therefore, muscular work is required in order to expel air from the lungs. Blebs, bullae and large air cysts which communicate poorly or not at all with the tracheobronchial tree are resistant to deformation and as a result greatly restrict the movements of breathing or increase the work demanded by these movements. Furthermore, the position of constant hyperinflation of the chest which is generally adopted by the emphysematous patient serves to diminish the motive power of the muscles of respiration by reducing their mechanical advantage. The diaphragm, already low, cannot descend much further. Contraction of this muscle serves not to increase the thoracic volume but merely tends to pull in the lower ribs. The intercostal muscles controlling the lower ribs, already shortened, have little remaining contractility. Lax abdominal musculature often seen in this disease further accentuates the impaired diaphragmatic action by failing to force the diaphragm up during expiration. The work required in breathing is thus increased simultaneously with a reduction in the ability of the chest bellows to do the work. In

this connection the importance of bronchiolar obstruction must be re-emphasized. Many patients with severe emphysema who are found on examination to have a markedly reduced maximum breathing capacity will demonstrate significant improvement on spirometry following the administration of a bronchodilator drug. (Fig. 1.) A similar beneficial effect will also be noted clinically in many instances, thus emphasizing that although the chest mechanics in the disease are altered so as to reduce the efficiency of the muscles of respiration, equally or more important is the increase in work required of breathing occasioned by bronchiolar narrowing.

The most important end result of these changes is the reduction of the breathing reserve¹⁹ which ensues, for herein lies the explanation of dyspnea in this disease. The occurrence of this symptom under most circumstances appears to depend not upon the amount of ventilatory work being done, i.e., the actual ventilation, but upon the relationship of this ventilation to what the chest bellows is capable of doing, i.e., the ventilatory capacity. This relationship is conveniently expressed by the concept of breathing reserve, which is the difference between the ventilatory capacity, measured as maximum breathing capacity, and the actual ventilation under consideration. Thus if the maximum breathing capacity were measured to be 100 L. per minute and the ventilation during the activity under consideration were 10 L. per minute, the breathing reserve would be 90 L. per minute or, expressed differently, 90 per cent of the maximum breathing capacity. In normal individuals as well as in most individuals with pulmonary disease dyspnea will be experienced when the breathing reserve is lower than 60 to 70 per cent of the maximum breathing capacity.¹⁹ Even though ventilation may be excessive, if maximum breathing capacity is so large that breathing reserve is greater than this general range, dyspnea is usually absent. Actually in emphysema the critical level is somewhat lower than this.¹ Nevertheless it is apparent that dyspnea can result from an increase in the ventilatory requirement or a decrease in the ventilatory capacity since either will bring about a reduction in the breathing reserve. Dyspnea in pulmonary emphysema is due chiefly to reduction in the ventilatory capacity because any hyperventilation which occurs is usually relatively slight.

In addition to being the major cause of dys-

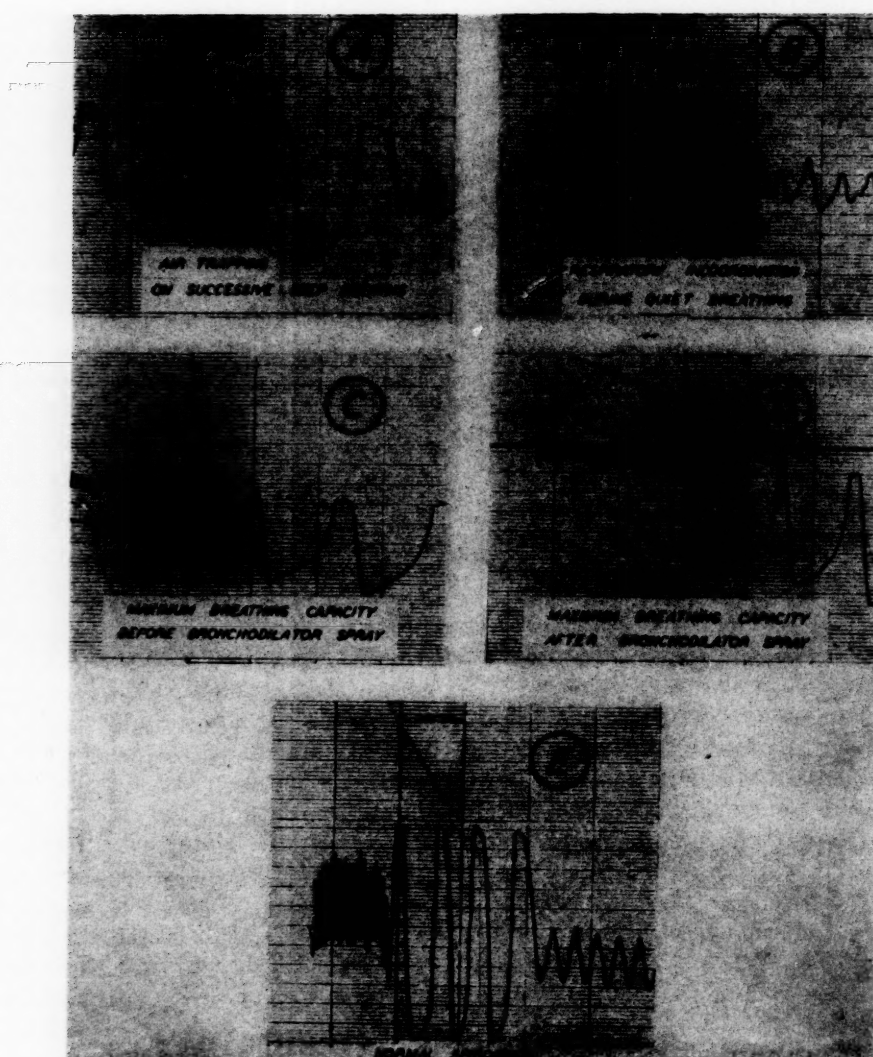


FIG. 1. Portions of various spirograms selected because they show certain abnormalities characteristic of pulmonary emphysema. These tracings move from right to left, with inspiration upward, and demonstrate the following: A, marked air trapping in a twenty-seven year old female, indicated by the progressive reduction in the amount of air expelled from the lungs after successive deep breaths. B, incoordination of respiratory movements during quiet breathing in a forty-six year old male indicated by marked irregularities in the tracing and variation in the mid-position of the chest, i. e., the position at the end of expiration. C, reduction in maximum breathing capacity in this patient with small tidal air during rapid breathing; note also that maximum breathing capacity is performed in the high inspiratory position. D, improvement in maximum breathing capacity in the same patient after use of a bronchodilator spray, with greater frequency and greater depth of respirations. E, a normal spiogram; note the shorter duration of expiration here in contrast to that in the emphysematous patients, the absence of air trapping, the median chest position during maximum breathing capacity determination, and the size of the tidal air at this time.

pnea, reduction in ventilatory capacity is significant from another point of view, namely, that of gas exchange. As will be discussed later the ventilatory capacity determines in large measure the adequacy of certain mechanisms which serve to compensate for disordered pulmonary gas exchange.

Distribution of Air and Blood in the Lungs—Gas Exchange. In addition to exerting the profound effects upon the mechanics of breathing noted previously, pulmonary emphysema further impairs the function of the lungs by interfering with the processes of gas exchange. In contradistinction, however, to the disturbances in lung volumes and in mechanics of breathing the effects of altered gas exchange are not, as a rule, readily apparent clinically, and recourse must be had to laboratory technics if abnormalities in this sphere are to be detected early.

Since the major function of the lungs is to effect an exchange of oxygen and carbon dioxide between mixed venous blood and the outside air, the most reasonable gauges of the adequacy of the entire process of gas exchange would appear to be, first, the composition of the major end product, i.e., the arterial blood as an index of the over-all effectiveness of the process and, second, the amount of ventilation required in this gas exchange as an index of the efficiency of the process. Accordingly, the finding of arterial blood not fully saturated with oxygen or with a higher than normal carbon dioxide partial pressure is direct evidence of defective gas exchange. Similarly, the finding of hyperventilation, with an accompanying reduction in the efficiency of breathing with respect to the amount of oxygen or carbon dioxide exchanged per unit of ventilation, is also evidence of defective gas exchange in the strict sense since this hyperventilation means that the process is not normally efficient.

The majority of patients with emphysema severe enough to produce symptoms exhibit some or all of these manifestations of defective gas exchange. Of sixty-eight patients studied by Baldwin, Cournand and Richards¹ forty-three were found to have significant arterial anoxia (oxygen saturation less than 92 per cent) after a short standard exercise. Of these patients twenty-four were found to have, in addition, significant hypercapnia (arterial $p\text{CO}_2^*$ greater than 48 mm. Hg). Hyperventilation with an accompanying reduction in oxygen utilization

rate occurred in the majority of patients. In one group, however, despite marked arterial blood abnormalities hyperventilation was not observed. The reason for the occurrence in some patients and not in others will be discussed presently. More recent work,²⁰ utilizing oximetric determinations of arterial oxygen saturation at rest, during as well as after exercise indicates that even more pronounced changes in arterial saturation may occur at the end of the standard one-minute exercise in emphysema and implies also that samples of arterial blood secured during the first minute of recovery may not reflect the maximum degree of impaired gas exchange that develops.

The factors involved in pulmonary gas exchange can be divided into two main categories: those concerned with the distribution of inhaled air and mixed venous blood to the alveoli, and those concerned with the diffusion of oxygen from alveolar air to capillary blood. All these factors are affected by emphysema. That inhaled air is unevenly distributed to the alveoli in pulmonary emphysema has been demonstrated by various direct methods.⁶⁻¹⁰ It seems likely that this occurs as a result of unequal bronchial or bronchiolar narrowing, local variations in distensibility due to non-homogeneous loss of elasticity in various portions of the lung, and the presence of air cysts, blebs and bullae poorly communicating with the tracheobronchial tree.

It has not, however, been shown directly by physiologic or other means that in emphysema there is uneven distribution of blood to the alveoli, nor does the frequent pathologic finding of ruptured alveolar septa without visible capillaries support this concept strongly, for it is not possible to determine from this histologic appearance what the circulation during life might have been. Recently developed injection studies of the pulmonary blood vessels and tracheobronchial tree do suggest, however, that circulation as well as air distribution is uneven in the emphysematous lung.

It is evident, however, from physiologic findings that imbalance in alveolar ventilation-perfusion relationships is a characteristic feature of emphysema^{15,21,22} and is the major cause of defective gas exchange in this disease.

Ventilation of alveoli that are poorly perfused with blood is inefficient ventilation. The blood that perfuses these alveoli becomes fully oxygenated and probably excessively depleted of

* Stands for partial pressure of carbon dioxide.

carbon dioxide,* but the quantity of blood flow is so small that the total gas exchange in these alveoli is slight and a greater than normal burden falls upon other alveoli. Furthermore, since little oxygen is removed from or carbon dioxide added to air ventilating these alveoli, this ventilation is similar to ventilation of the anatomic dead space and may be termed dead-space-like ventilation. Adequate carbon dioxide elimination as evidenced by a normal arterial $p\text{CO}_2$ can occur in the presence of excessive dead-space-like ventilation only when the normally perfused alveoli are hyperventilated. If hyperventilation of these alveoli does not occur, carbon dioxide retention will take place.²³ Adequate oxygen intake with only minimal reduction in arterial oxygen saturation can occur without hyperventilation in the presence of considerable dead-space-like ventilation. Accordingly, the only significant effect of increased dead-space-like ventilation upon gas exchange is a tendency toward carbon dioxide retention.

Perfusion of alveoli that are poorly ventilated results in arterial anoxia as well as a tendency toward carbon dioxide retention. This is due to the fact that not enough oxygen is added to or carbon dioxide removed from these alveoli by the process of alveolar ventilation. Blood perfusing these alveoli cannot, therefore, be fully oxygenated or normally depleted of carbon dioxide. The effect upon the arterial blood composition of mixing this fraction of capillary blood with the remainder is similar to that of a true veno-arterial shunt, the magnitude of which can be calculated.¹⁷ This virtual shunt plus the true anatomic shunt resulting from bronchial veins, thebesian veins, etc., has been termed the venous admixture.¹⁴ Carbon dioxide retention may not be realized if sufficient hyperventilation of remaining, well ventilated, well perfused alveoli occurs. Arterial anoxia cannot, however, be corrected to any significant degree by hyperventilation of normal alveoli.

One other aspect of gas exchange in emphysema must be considered, namely, that concerned with diffusion of oxygen across the alveolar capillary membrane. In addition to being dependent upon the physicochemical characteristics of the alveolar capillary membrane, the oxygen diffusing capacity of the lungs is also dependent upon the total area of the

membrane, i.e., the total surface provided by the pulmonary capillary bed. In emphysema the oxygen diffusing capacity is often found to be reduced when measured by the Riley method.¹⁷ That this is not due to any change in the character of the alveolar capillary membrane seems likely from the histologic appearance of the emphysematous lung; it seems more reasonable that this is due to a reduction in the size of the total vascular bed. This reduction in the oxygen diffusing capacity doubtless has little effect upon gas exchange in emphysema under conditions of rest. The marked decrease in arterial oxygen saturation observed during exercise,²⁰ however, in some patients with emphysema is probably in part a reflection of reduction in the oxygen diffusing capacity.

The importance of alveolar ventilation-perfusion relationships in the phenomena of gas exchange have been emphasized, and the role of hyperventilation in compensation for defective carbon dioxide exchange has been indicated. To be considered now is the effect of impaired gas exchange in emphysema upon pulmonary ventilation and its regulation.

Influence of Gas Exchange upon the Nervous Regulation of Ventilation. As in the normal individual, pulmonary ventilation in the patient with emphysema is regulated on the one hand by mechanisms concerned with meeting the metabolic and homeostatic needs of the body²⁴ and, on the other hand, by mechanisms largely reflex in nature, e.g., stretch reflexes such as the Hering-Breuer reflex, various proprioceptive reflexes arising in the other parts of the body, etc. These will not be considered here since they are not concerned with the problem of gas exchange. The medullary respiratory center of the patient with emphysema, just as in the normal man, is ordinarily exquisitely sensitive to changes in arterial $p\text{CO}_2$, responding to even a very small increment with an increase in the respiratory stimulus which has been termed by Bjurstedt²⁵ "centrogenic drive." Similarly, the aortic and carotid glomi in the patient with emphysema probably respond to arterial anoxia as they do in the normal individual, i.e., acute anoxia, if severe enough, results in an increased respiratory stimulus arising in these bodies. When this stimulus transmitted through the medullary center exerts an effect upon ventilation, it may be termed "chemoreflex drive."²⁶

Inasmuch as the centrogenic drive is normally a much stronger one than is the chemoreflex, the

* This is due to the different characteristics of the carbon dioxide and oxygen dissociation curves. For demonstration see Figure 9.¹⁶

hyperventilation at rest observed in most cases of pulmonary emphysema is due chiefly to an increased centrogenic drive despite the possible presence of mild anoxia. Thus in the presence of both carbon dioxide retention and anoxia, the stimulus to hyperventilation, if present, is probably due to carbon dioxide retention unless the anoxia is quite severe. The hyperventilation observed in emphysematous patients during acute exercise may, however, be due in part to arterial anoxia with its resultant chemoreflex drive because, as mentioned previously, anoxia may reach strikingly low levels during acute exercise in this disease.

When ventilatory capacity is so inadequate as to be unable to maintain sufficient compensatory hyperventilation under an increase in either centrogenic or chemoreflex drive, true carbon dioxide retention occurs and the partial pressure of this gas in arterial blood increases. An increase in arterial $p\text{CO}_2$, if sustained, is regularly associated with a compensatory increase in alkaline reserve. This increase in the buffering capacity of the plasma has the unfavorable effect of decreasing the sensitivity of the respiratory center to the carbon dioxide stimulus. The result is that with increasing CO_2 retention in emphysema the centrogenic drive to ventilation tends to decrease, and as it does the chemoreflex drive due to the accompanying arterial anoxia increases in importance. Thus insidiously a vicious cycle begins. Inadequate ventilation leads to carbon dioxide retention which brings about an increase in the alkaline reserve. There follows a decrease in the sensitivity of the medullary center to carbon dioxide whereby ventilation is reduced still further and more carbon dioxide retention is promoted. Finally, a stage is reached wherein the major portion of the respiratory stimulus is a result of arterial anoxia.

At this stage hyperventilation is usually no longer observed. In fact, hypoventilation during all phases of activity is a characteristic finding accompanying those forms of emphysema with severe arterial anoxia and an abnormally high carbon dioxide tension.¹ The intimate details of this failure of severe anoxia in this instance to induce hyperventilation are not clear. In some of these cases mechanical disturbances, as described above, impose an absolute restriction upon the amount of pulmonary ventilation that can be achieved; but in the most severely anoxic subjects there is usually some breathing reserve, even in exercise, that has not been called upon.

In this respect the concomitant presence of moderate respiratory acidosis may be of some importance in view of Bjurstedt's²⁵ conclusion that acute hypoxic hyperventilation is potentiated by the respiratory alkalosis which it engenders. Furthermore, prolonged dependency upon the chemoreflex drive, which in normal man is a mechanism of temporary activity only, might result in diminution in its strength.

This state of the disease then is one of breakdown of the mechanisms which are compensatory for defective gas exchange, and these patients represent difficult problems in therapy. If oxygen is given in an attempt to relieve dyspnea and cyanosis, the increase in arterial saturation which will occur may diminish the chemoreflex drive and may result in further hypoventilation and therefore more carbon dioxide retention. Severe gaseous acidosis may occur and carbon dioxide narcosis appear. Oxygen, if administered to these patients, should be given only intermittently and sparingly. It has been reported²⁶ that by the use of an intermittent positive pressure respirator in the administration of oxygen to these patients sufficient alveolar ventilation will be maintained to prevent carbon dioxide retention.

PHYSIOLOGIC CLASSIFICATION OF EMPHYSEMA WITH ILLUSTRATIVE CASES

The effects of chronic pulmonary emphysema upon the function of the lungs have thus far been described in general terms, separate consideration being given the abnormalities encountered in the lung volumes, mechanics of breathing and the phenomena of gas exchange. In emphysematous patients physiologic disturbances in each of these categories may be present to greater or lesser degree and wide variation in clinical patterns results. It is possible, however, to classify the patients into several broad groupings based upon similarities in the pattern of dysfunction displayed. Such a classification has been proposed recently by Baldwin, Cournand and Richards¹ who separated a large number of patients into four groups according to criteria selected, first, to set apart patients with only pulmonary insufficiency from those with combined pulmonary and cardiocirculatory insufficiency and, second, to divide those with purely pulmonary insufficiency into three groups depending upon the degree of impairment of gas exchange. The main physiologic characteristics of these groups will be summarized and repre-

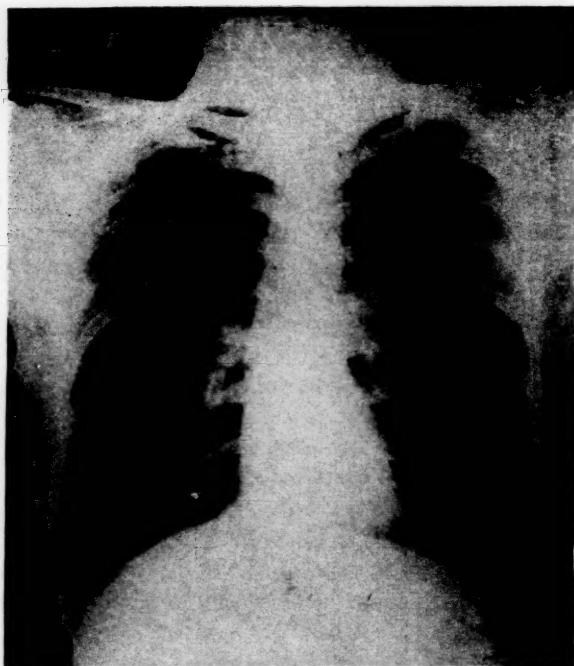


FIG. 2. Case 1. X-ray of the chest.

sentative cases in each group will be discussed, with emphasis on the newer types of measurements which permit an analysis of mechanisms involved in gas exchange. Finally, brief comments will be made concerning the essential features of therapy in each group.

Group 1

Main Physiologic Characteristics. In this group are placed emphysematous patients who are found to have an arterial oxygen saturation above 92 per cent following the standard exercise test. These patients have more or less severe impairment of ventilatory function and moderate disturbance of intrapulmonary air distribution. Adequate alveolar ventilation is maintained, however, by means of compensatory hyperventilation, to a degree sufficient to overcome this distributional defect and no retention of carbon dioxide occurs. It is well realized that the criterion of 92 per cent arterial saturation, selected on the basis of statistical data,²⁷ is an arbitrary one and that furthermore this level is abnormally low. It does not, however, represent a serious degree of anoxia. The major disability of this group is, therefore, *ventilatory insufficiency*, i.e., reduction in breathing reserve to such an extent as to limit physical activity and cause dyspnea.

CASE 1. A typical example of this group was a forty-four year old male (M. B.) who com-

plained of increasing exertional dyspnea of five years' duration, which was especially severe on exposure to cold at which time wheezing was noticeable. There was a history of mild non-productive cough during the winter months for many years and in the recent past there had been frequent respiratory infections, the latest of which had occasioned his admission to the hospital. On physical examination no cyanosis was apparent. The chest was hyperinflated and hyperresonant, and breath sounds were diminished throughout. Faint high pitched wheezes were heard at both lung bases on expiration and fine rales were audible over the dorsal segment of the right lower lobe. The heart was not abnormal. An x-ray of the chest (Fig. 2) revealed hyperaeration of the lung fields with some bulla formation and low diaphragms. The heart shadow was small.

The results of the physiologic studies (Table 1) are characteristic of this group. There was a moderate increase in total lung capacity and in the ratio of residual volume to total lung capacity. The maximum breathing capacity was only moderately reduced and resting ventilation was abnormally large. The index of intrapulmonary mixing was elevated. Arterial oxygen saturation was normal after strenuous bicycle exercise as well as at rest and arterial $p\text{CO}_2$ was not increased. Further evidence of normal over-all alveolar ventilation was provided by the finding of an increased alveolar $p\text{O}_2$.*

Adequate although inefficient gas exchange was maintained in this patient by means of compensatory hyperventilation, in the presence of excessive dead-space-like ventilation, a slight increase in estimated venous admixture and a slight reduction in estimated oxygen diffusing capacity.

The major disability of this patient was, therefore, ventilatory insufficiency.

Therapy. Therapy in this group of patients consists chiefly in measures designed to maintain and improve the ventilatory capacity. Respiratory infections should be carefully avoided and vigorously treated if contracted. The routine use of bronchodilator drugs, especially those designed for inhalational use, is often of great help. If the diaphragms are low in position and markedly flattened, considerable improvement in vital capacity and in maximum breathing capacity may be obtained by a well fitted lower abdominal belt. Oxygen therapy is not

* Stands for partial pressure of oxygen.

indicated in this group and activity need not be restricted.

Groups 2 and 3

Main Physiologic Characteristics. In group 2 are placed those patients with an oxygen saturation in the arterial blood below 92 per cent and carbon dioxide tension below 48 mm. Hg following the standard exercise test, while in group 3 are those with an arterial oxygen saturation below 92 per cent and a carbon dioxide tension above 48 mm. Hg following the standard exercise test. They are discussed together here since the pattern of pulmonary dysfunction displayed by these groups is essentially the same.

In these patients reduction in ventilatory function is more marked than in group 1 as is the degree of impairment of gas exchange. In some patients, by means of compensatory hyperventilation, carbon dioxide retention is prevented. In others, however, carbon dioxide retention does occur, and there is no sharp dividing line to separate one group from the other. Furthermore, the level of arterial $p\text{CO}_2$ after exercise in a single patient may vary from time to time depending upon alterations in the degree of bronchospasm. In all patients, however, arterial anoxia after exercise is present and is more severe in patients of group 3.

These two groups suffer from *alveolo-respiratory insufficiency*, i.e., ineffective gas exchange of varying severity in addition to ventilatory insufficiency.

Two cases will be presented to illustrate the findings in these groups, one with marked emphysema and a large total lung capacity, the other with more severe functional impairment but with a small total lung capacity and a large solitary air cyst.

CASE II. A thirty-three year old male (C. H.) complained of severe dyspnea on exertion. There was a history of recurrent bronchial asthma beginning five years before admission which responded to treatment and occasioned no serious disability until three years before admission, when the onset of unrelieved, progressive dyspnea on exertion was noted. As a result of this, activity was greatly limited at the time of study. There was no history of recurrent respiratory infections. Cough was slight and productive of only small amounts of white sputum. On physical examination no cyanosis was apparent. The thorax was held in the hyperinflated position and diaphragmatic motion was small. The chest



FIG. 3. Case II. X-ray of the chest.

was resonant throughout, breath sounds were quite distant and expiration was prolonged. Wheezes but no rales were audible throughout both lungs. The heart was not abnormal. An x-ray of the chest (Fig. 3) revealed hyperaeration of the lung fields with considerable bulla formation, especially at the bases, and the diaphragms were low. The heart was not enlarged in its transverse diameter but the main pulmonary artery was slightly prominent.

Physiologic studies (Table 1) revealed findings typical of group 2. There was a moderate increase in total lung capacity with a marked increase in the ratio of residual volume to total capacity. The maximum breathing capacity was reduced to such an extent that breathing reserve on standard exercise had reached the vanishing point. Moderate hyperventilation was present at rest. The index of intrapulmonary mixing was increased. A slight arterial anoxia at rest became much more severe on exercise and arterial $p\text{CO}_2$ was slightly increased at rest. Effective alveolar $p\text{O}_2$ remained normal.

These findings are particularly interesting in view of the other data relating to alveolar ventilation-perfusion relationships and the diffusion of oxygen across the alveolar capillary membrane. The large size of the physiologic dead space and, to a lesser extent, the slightly increased estimated venous admixture resulted in moderate carbon dioxide retention in this case



FIG. 4. Case III. X-ray of the chest.

because adequate compensatory hyperventilation was prevented by the marked reduction in ventilatory capacity. Slight arterial unsaturation at rest was doubtless the result of perfusion of poorly ventilated alveoli while the marked decrease noted after exercise was probably related to the reduction in estimated oxygen diffusing capacity as well as alveolar hypoventilation. From the nature of the lesion in pulmonary emphysema it would seem that the low oxygen diffusing capacity is a result of a reduction in the area of the alveolar-capillary interface rather than thickening of the alveolo-capillary membrane.

This case illustrates the physiologic changes resulting from moderately advanced emphysema in which severe restriction in ventilatory capacity prevented effective compensation for abnormalities in alveolar ventilation-perfusion relationships that were only moderately severe.

CASE III. A fifty-three year old female (J. W.) complained of incapacitating dyspnea of ten years' duration, associated with chronic cough, always productive of large amounts of mucopurulent sputum. There was a history of frequent respiratory infections beginning in childhood and chronic pan-sinusitis had been present for many years. One year prior to study, according to the patient, there had been an episode of mild congestive heart failure which apparently responded well to digitalis. Details of this illness

are, however, lacking. The recent onset of an acute upper respiratory tract infection had been followed by a sharp increase in sputum production and extreme dyspnea which had necessitated admission to the hospital. On physical examination the patient was seen to be somewhat cachectic and in extreme respiratory distress which was accentuated by frequent coughing paroxysms during which large amounts of tenacious green sputum were raised. Cyanosis was intense. The chest was hyperinflated and diaphragms were low. On inspiration the lower ribs and supraclavicular spaces were retracted as the entire thorax was lifted upward with strong contractions of the accessory muscles of respiration. Expiration was prolonged. The chest was hyperresonant throughout and breath sounds everywhere markedly reduced. Coarse rhonchi and inspiratory rales were audible in all areas. The heart was not enlarged and its rhythm was regular. The sounds, though distant, were of good quality, the second sound being loudest in the pulmonic area. No murmurs were heard. The liver was slightly enlarged and tender but there was no edema. An x-ray examination of the chest (Fig. 4) revealed, in addition to marked emphysematous changes, the presence of a very large air cyst in the region of the right upper lobe. The heart shadow was small. Following treatment with antibiotics and bronchodilator drugs the acute respiratory infection gradually subsided. Oxygen therapy was continuous during the first weeks of hospitalization and only with some difficulty was the patient weaned away from it. At no time, however, did the syndrome of carbon dioxide narcosis appear.

Physiologic studies (Table 1) performed several weeks after admission to the hospital revealed the total lung capacity to be considerably smaller than predicted while the ratio of residual volume to total lung capacity was increased. Maximum breathing capacity was reduced but not to the severe degree seen in Case II. There was only slight resting hyperventilation. The index of intrapulmonary mixing was considerably increased. The standard exercise test could not be performed but there was considerable arterial anoxia as well as hypercapnia at rest. Effective alveolar pO_2 was reduced.

Of interest is the reduction in total lung capacity in the presence of obvious hyperinflation of the chest on x-ray and physical examination. The most likely reason for this discrepancy is

failure of the large air cyst in the right upper lobe to communicate well with the tracheobronchial tree, thus becoming inaccessible to physiologic measurement. The reduction in resting arterial oxygen saturation was probably due to perfusion of poorly ventilated alveoli in view of the in-

volume measurements and poses the question whether part of the apparent dysfunction at the time of study might not have been due to oxygen therapy beforehand.

Therapy. Therapy of patients in groups 2 and 3 embodies the principles outlined for group 1

TABLE I
PHYSIOLOGIC MEASUREMENTS IN FIVE PATIENTS WITH CHRONIC PULMONARY
EMPHYSEMA ILLUSTRATING DIFFERENT PATTERNS OF RESPIRATORY FUNCTION

Measurement	Case I		Case II		Case III		Case IV		Case V		
	Pre- dicted	Ob- served	Pre- dicted	Ob- served	Pre- dicted	Ob- served	Pre- dicted	Ob- served	Pre- dicted	Observed	
										First Study*	Second Study†
Total lung capacity, cc.	4610	5470	5800	7145	4510	3659	5240	3989	3920	4392	3870
Residual volume, cc.	1125	2333	1150	4935	1170	2183	1280	2921	1015	1824	1371
Residual volume Total lung capacity $\times 100$	25	45	25	69	30	60	30	74	30	42	36
Maximum breathing capacity, L./min.	91	49	120	19	62	24	84	13	70	35	48
Ventilation, L./min./sq. m. b. s.‡											
At rest.	3.1	6.7	3.6	6.2	3.4	4.5	3.9	5.8	3.4	2.7	6.1
During 1 minute standard exercise.			11.0	12.0					11.4	8.5	9.8
Breathing reserve, L./min. during 1 minute standard exercise.			101	0					52	22	34
Index of intrapulmonary mixing, N ₂ %	<2.5	5.8		5.7		8.1		7.9		3.1	1.1
Arterial oxygen saturation, %											
At rest.	>96	96		91		84		63		78	94
During 1st minute recovery.	>96	95		73				48		66	74
Arterial pCO ₂ at rest, mm. Hg.	38	34		47		58		63		53	44
Effective alveolar pO ₂ , mm. Hg.	103	121		103		83		78		80	106
Dead space ventilation, % of tidal air.	<30	49		52		39		53		35	32
Venous admixture, % of cardiac output	< 6	10		11		26		46		29	15
Oxygen diffusing capacity (D _{O2}), cc./ min./mm. Hg mean pressure gradient	>15	12		6		6		5		6	9

* Indicates observations made during state of congestive failure.

† Indicates observations made after recovery from failure.

‡ sq. m. b. s. = square meter of body surface area.

crease in estimated venous admixture. That this was probably the chief cause of arterial hypercapnia, as well, is indicated by the fact that there was only a moderate increase in dead space ventilation. Further evidence of inadequate over-all alveolar ventilation is provided by the low value for effective alveolar pO₂ which was derived. As in the previous case the oxygen diffusing capacity was reduced.

The minimal hyperventilation in the presence of a markedly increased arterial pCO₂ and a fair ventilatory capacity suggests the possibility that reduction in centrogenic drive due to increased alkaline reserve might have resulted from prolonged oxygen therapy during the acute illness but proof of this is lacking.

In summary, this is a case in which the degree of ventilatory insufficiency depended heavily upon the state of the bronchial disease. It illustrates the effect of a large air cyst upon lung

with added features. These patients may develop pulmonary arterial hypertension during exercise which may be related to anoxia²⁸ and therefore should be enjoined from excessive activity in view of the possible increased cardiac work which may be brought about. Since ventilatory capacity is, as a rule, more seriously impaired than in the preceding group, the use of bronchodilator drugs must often be supplemented by other measures designed to improve ventilatory capacity. The use of abdominal supports as above described may be of real aid in increasing the range of diaphragmatic motion in some patients. Breathing exercises and instruction in diaphragmatic breathing are found beneficial to others. Short periods of oxygen breathing several times a day are helpful in those patients who easily become anoxic, often resulting in subjective improvement, diminution in weakness and fatigability, improvement in appetite and

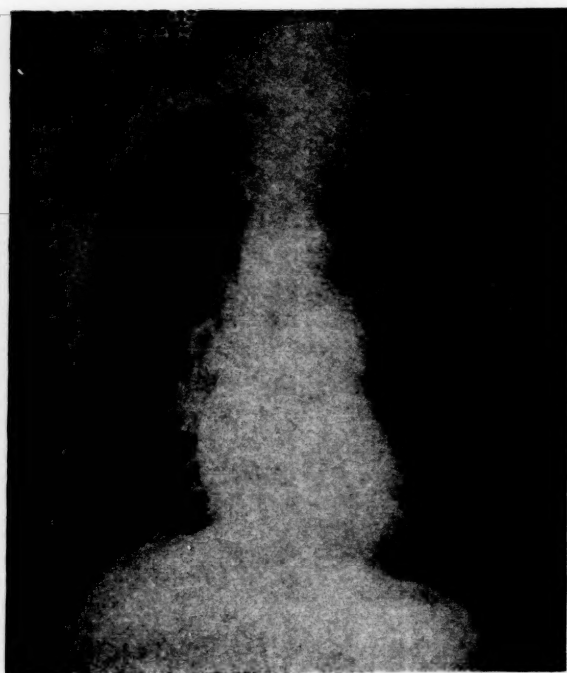


FIG. 5. Case iv. X-ray of the chest.

increased sense of well being. In the presence of acute respiratory infections and resultant grave impairment of pulmonary function oxygen therapy may be mandatory until the infection has been overcome. In general, however, continuous administration should be avoided because habituation to oxygen therapy is easily acquired and, furthermore, carbon dioxide retention might occur to a degree sufficient to cause a depression of the centrogenic drive to ventilation. Since large, poorly communicating air cysts such as that observed in Case III (J. W.) often exert deleterious effects upon ventilatory function, surgical removal is often worth considering. This procedure in patients with emphysema in the remaining lung may, however, be followed by greater impairment of pulmonary function than existed previously. The special problems in this connection have been discussed in a recent publication.²⁹

Group 4

Main Physiologic Characteristics. In this group are those patients who have right-sided congestive heart failure in addition to pulmonary insufficiency. The degree of ventilatory and alveolo-respiratory insufficiency is similar to that in groups 2 and 3 but extreme variations may be noted. In contrast to the patients in the first three groups there is often a lack of compensatory hyperventilation during most phases

of activity, even in the presence of a fairly large breathing reserve. This is due, at least in part, to the disturbance in the nature of the respiratory stimulus which is of common occurrence in this group. In association with this tendency toward hypoventilation carbon dioxide retention, acidosis and arterial anoxia are quite severe. The mechanisms concerned with this hypoventilation have been discussed previously.

Two cases will be presented in order to illustrate the usual respiratory findings, first, in cases in which the occurrence of congestive heart failure is secondary to marked emphysema of long duration and, second, in those in which congestive heart failure is secondary to mild emphysema, but with intense bronchospasm, bronchial obstruction and the resulting arterial anoxia.

CASE IV. A fifty-three year old male (E. W.) entered the hospital complaining of severe exertional dyspnea of ten years' duration. He stated that cyanosis of the lips and nailbeds had been apparent for several years and slight ankle edema had been present intermittently for one year. There was a history of very frequent attacks of acute bronchitis for about twenty years with a chronic cough always productive of large amounts of green, non-foul, non-bloody sputum. On physical examination intense cyanosis was apparent. The thorax was held in the hyperinflated position and breathing was labored with marked obstructive signs. The lungs were hyperresonant, breath sounds were diminished and moist rales were heard throughout. Expiration was prolonged and scattered wheezes were present. The heart was slightly enlarged to the left, its rhythm was regular and a presystolic gallop was noted. The second sound was loudest in the pulmonic area and a systolic murmur was heard over the xiphoid. The liver was slightly enlarged but not tender. An x-ray examination of the chest (Fig. 5) revealed pronounced emphysematous changes bilaterally with increased vascular shadows at both roots. The heart was enlarged in its transverse diameter and the pulmonary artery and its main branches were prominent.

Because of the appearance of ankle edema while in the hospital the patient was digitalized but treatment with bronchodilators and antibiotics to combat bronchiolar obstruction and anoxia was intermittent and not intensive. After a short period of apparent improvement the course was progressively downhill; death oc-

curred some six and one-half months after admission to the hospital.

At necropsy the lungs were found to be markedly emphysematous with bulla formation. There was moderate pulmonary atherosclerosis and arteriolosclerosis and some alveolar septa appeared to contain engorged capillaries. Other septa appeared fragmented and avascular and it was not possible to estimate, from examination of the histologic sections, the area of the capillary surface that had existed during life. There was a slight amount of fibrous tissue around some of the bronchioles but no reduction in bronchiolar caliber could be made out. The heart weighed 350 gm. and the pulmonary artery, right ventricle and right atrium were greatly dilated. The left atrium and ventricle were minimally dilated. The myocardium of the right ventricle measured 3 to 5 mm. in thickness. All valves were normal and the coronary arteries minimally atherosclerotic.

Physiologic studies (Table 1) revealed the total lung capacity to be considerably reduced with a marked increase in the ratio of residual volume to total lung capacity. Maximum breathing capacity was extremely small. The index of intrapulmonary mixing was greatly increased. Arterial oxygen saturation was very low at rest and on very mild exercise fell even lower. Resting arterial $p\text{CO}_2$ was high and effective alveolar $p\text{O}_2$ reduced. Imbalance in alveolar ventilation-perfusion relationships was extreme in this case as was reduction in oxygen diffusing capacity. Probably equally important, however, in the development of the severe pattern of alveolo-respiratory insufficiency was the extreme reduction in ventilatory capacity which made compensatory hyperventilation impossible. The small total lung capacity probably reflects the presence of emphysematous bullae, found at necropsy, not communicating with the tracheobronchial tree.

It is noteworthy that this patient, with considerable obstructive emphysema during life was found to have no bronchial or bronchiolar obstruction at necropsy, which serves to emphasize the role of bronchospasm in this disease.

This case illustrates the development of chronic cor pulmonale in a patient with severe obstructive emphysema of very long duration in which extreme ventilatory insufficiency was associated with grave impairment of the mechanisms of gas exchange.

CASE V. A fifty-five year old female (A. D.)

entered the hospital because of ankle edema of one week's duration. She stated that she had had asthma for about twenty years characterized by paroxysmal attacks of wheezing dyspnea relieved by burning stramonium leaves. There had been mild dyspnea on exertion for many years but no orthopnea, paroxysmal nocturnal dyspnea or angina. Cough was denied. On physical examination intense cyanosis was obvious. The thorax was slightly hyperinflated and its excursions were small. There was slight dullness and a few rales at both lung bases, breath sounds were diminished and wheezes were heard throughout. Over the right middle lobe the breath sounds were particularly faint and crackling rales were audible. The heart was enlarged to the left, its rhythm was regular and the second sound was loudest in the pulmonic area. No murmurs were heard. The liver was moderately enlarged and there was pitting edema extending up to the knees. An x-ray of the chest (Fig. 6) demonstrated mottled infiltrations in the right middle lobe but no significant emphysematous changes. The heart was markedly enlarged in its transverse diameter. Additional history and older x-rays gave convincing evidence that the middle lobe infiltrate was the residuum of a pneumonitis which had been contracted five years previously.

Physiologic studies (Table 1) were performed on two occasions, the first after one week and the second after two months of intensive therapy. On the first study a slight increase in total lung capacity and in the ratio of residual volume to total lung capacity was noted. The maximum breathing capacity was only moderately reduced but, despite this, there was no hyperventilation in the presence of considerable arterial anoxia and hypercapnia. The absence of hyperventilation in all likelihood was the result of an alteration in the response of the respiratory center to physiologic stimuli. As evidenced by the value for physiologic dead space, ventilation of poorly perfused alveoli was not excessive. The estimated value for venous admixture, however, indicates that perfusion of poorly ventilated alveoli was probably excessive at this time. The fact that the index of intrapulmonary mixing was only slightly increased suggests that the alveolar hypoventilation in this case was of a more uniform type than in Cases III (J. W.) or IV (E. W.) although the net results in all three cases are comparable, an hypothesis in keeping with the minimal degree of emphysema and the maximum degree of bronchospasm in this case.

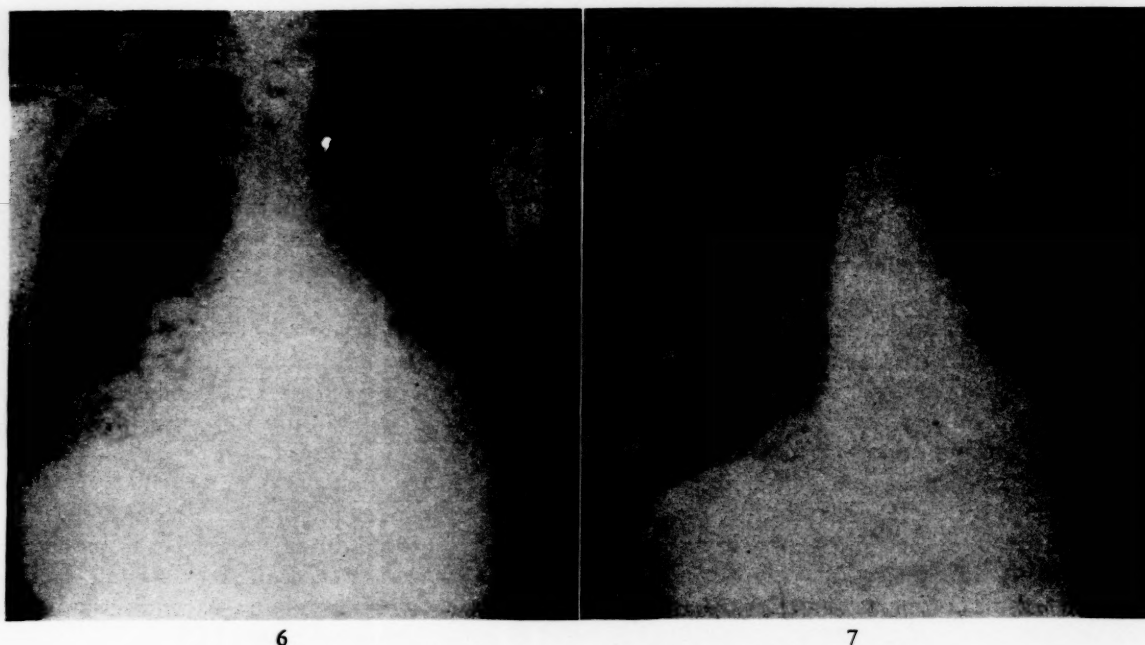


FIG. 6. Case v. X-ray of the chest at the time of the first physiologic studies.

FIG. 7. Case v. X-ray of the chest at the time of the second physiologic studies.

After prolonged and intensive treatment which included digitalization, very frequent use of bronchodilator sprays and several phlebotomies, considerable clinical improvement was noted with disappearance of all evidence of congestive heart failure, and slight reduction in the size of the heart shadow on x-ray of the chest. (Fig. 7.) At the time of this x-ray the second series of physiologic studies (Table 1) were performed. These studies revealed an even smaller degree of overdistention of the lungs than had been present at the time of the first study. In addition there was improvement in maximum breathing capacity, a normal oxygen saturation at rest, which fell to a low level on exercise, only a slight increase in arterial $p\text{CO}_2$ at rest and a definite improvement in effective alveolar $p\text{O}_2$. There seemed also to be some improvement in the response of the respiratory center to physiologic stimuli in that there was slight hyperventilation at rest and an increased amount of ventilation on exercise. At this time the physiologic dead space was practically normal and the venous admixture only slightly increased. Arterial oxygen unsaturation after exercise was probably related to the reduction in oxygen diffusing capacity, at least in part, although this degree of reduction in diffusing capacity is only moderate.

In summary, this case illustrates the occurrence of cor pulmonale in a patient with minimal

emphysema but with intense bronchospasm, arterial anoxia and hypercapnia, to which syndrome probably the term Ayerza's disease may be best applied. It further illustrates the beneficial effects which may be achieved through intensive and vigorous therapy. This patient in congestive heart failure as a result of severe pulmonary dysfunction at the time of the first study had so improved at the time of the second study that a classification of group 4 was no longer applicable.

Therapy. Treatment of patients in group 4 includes all the measures outlined in connection with the other groups plus the additional measures required by congestive heart failure. Particular emphasis must be placed on the intensive use of bronchodilator drugs and antibiotics to combat bronchospasm and bronchial infection. Bronchodilators must be used liberally and unceasingly. Continuous oxygen therapy should be avoided at all costs because of the danger of carbon dioxide narcosis. These patients characteristically have polycythemia and greatly increased blood volumes; and repeated phlebotomy is an important factor in therapy.^{30,31}

SUMMARY

1. The effects of chronic pulmonary emphysema upon the lung volume measurements, mechanics of breathing, pulmonary gas exchange

and nervous regulation of ventilation have been presented and discussed.

2. An attempt has been made to relate some of the physiologic disturbances to the pathologic findings and to the clinical picture in this disease.

3. The interrelationship between the various physiologic changes has been emphasized and four separate patterns of pulmonary insufficiency, previously reported, have been discussed briefly and illustrated by individual cases.

4. The important features of therapy have been outlined in each of the four patterns. Special emphasis has been placed upon the relief of arterial anoxia and carbon dioxide retention by correction of their main cause, i.e., inadequate alveolar ventilation rather than by oxygen therapy. The effect of oxygen inhalation upon the nervous regulation of ventilation has been discussed.

REFERENCES

- BALDWIN, E. DEF., Cournand, A. and Richards, D. W., Jr. Pulmonary insufficiency. III. A study of 122 cases of chronic pulmonary emphysema. *Medicine*, 28: 210, 1949.
- LOESCHKE, H. Störungen des Luftgehalts, p. 613. In *Handbuch der Speziellen Pathologischen Anatomie und Histologie* III/1. Berlin, 1928. Julius Springer.
- CHRISTIE, R. V. The elastic properties of the emphysematous lung and their clinical significance. *J. Clin. Investigation*, 13: 295, 1934.
- KNIPPING, H. W., LEWIS, W. and MONCRIEFF, A. Über die Dyspnoe. *Beitr. z. Klin. Tuberk.*, 79: 1, 1931.
- KNIPPING, H. W. Dyspnoea. *Beitr. z. Klin. Tuberk.*, 82: 133, 1932.
- NIELSEN, E. and SONNE, C. Zusammensetzung der Alveolarluft. *Ztschr. f. d. ges. exper. Med.*, 85: 46, 1932.
- SONNE, C. Die respiratorische Luftaustausch in den Lungen. *Ztschr. f. d. ges. exper. Med.*, 94: 13, 1934.
- ROELSEN, E. The composition of alveolar air investigated by fractional sampling. Comparative investigations in normal persons and patients with bronchial asthma and pulmonary emphysema. *Acta med. Scandinav.*, 98: 141, 1939.
- DARLING, R. C., Cournand, A. and Richards, D. W., Jr. Studies on the pulmonary mixture of gases. V. Forms of inadequate ventilation in normal and emphysematous lungs, analyzed by means of breathing pure oxygen. *J. Clin. Investigation*, 23: 55, 1944.
- FOWLER, W. S. Lung function studies. III. Uneven pulmonary ventilation in normal subjects and in patients with pulmonary disease. *J. Applied Physiol.*, 2: 283, 1949.
- HURTADO, A., KALTREIDER, N. L., FRAY, W. W., BROOKS, W. D. W. and McCANN, W. S. Studies in total pulmonary capacity and its subdivisions. VI. Observation on cases of obstructive pulmonary emphysema. *J. Clin. Investigation*, 13: 1027, 1934.
- HURTADO, A., KALTREIDER, N. L. and McCANN, W. S. Studies in total pulmonary capacity and its subdivisions. IX. Relationship to the oxygen saturation and carbon dioxide content of the arterial blood. *J. Clin. Investigation*, 14: 94, 1935.
- KALTREIDER, N. L. and McCANN, W. S. Respiratory response during exercise in pulmonary fibrosis and emphysema. *J. Clin. Investigation*, 16: 23, 1937.
- LILIENTHAL, J. L., JR., RILEY, R. L., PROEMMEL, D. D. and FRANKE, R. E. An experimental analysis in man of the oxygen pressure gradient from alveolar air to arterial blood during rest and exercise at sea level and at altitude. *Am. J. Physiol.*, 147: 199, 1946.
- RILEY, R. L. and Cournand, A. "Ideal" alveolar air and the analysis of ventilation-perfusion relationships in the lungs. *J. Applied Physiol.*, 1: 825, 1949.
- RILEY, R. L. and Cournand, A. Analysis of factors affecting the concentration of oxygen and carbon dioxide in the gas and blood of the lungs. I. Theory. *J. Applied Physiol.*, (in press).
- RILEY, R. L., DONALD, K. and Cournand, A. Analysis of factors affecting the concentration of oxygen and carbon dioxide in the gas and blood of the lungs. II. Methods. *J. Applied Physiol.*, (in press).
- Cournand, A., BROCK, H. J., RAPPAPORT, I. and Richards, D. W., Jr. Disturbance of action of respiratory muscles as a contributory cause of dyspnea. *Arch. Int. Med.*, 57: 1008, 1936.
- Cournand, A. and Richards, D. W., Jr. Pulmonary insufficiency. I. Discussion of a physiological classification and presentation of clinical tests. *Am. Rev. Tuberc.*, 44: 26, 1941.
- DOUGLAS, J. and Cournand, A. To be published.
- Cournand, A. Cardiopulmonary function in chronic pulmonary disease. *Harvey Lect.*, 1950-51. (In press.)
- DONALD, K., RILEY, R. L., RENZETTI, A. and Cournand, A. Analysis of factors affecting the concentration of oxygen and carbon dioxide in the gas and blood of the lungs. III. Results in patients with pulmonary disease. To be published.
- ROSSIER, P. H. and BLICKENSTORFER, E. Espace mort et hyperventilation. *Helvet. med. acta*, 13: 328, 1946.
- PITTS, R. F. Regulation of Respiration, chap., 42. In Fulton, J. F. ed. *A Textbook of Physiology*, 16th ed. Philadelphia, 1949. W. B. Saunders Co.
- BJURSTEDT, A. G. H. Interaction of centrogenic and chemoreflex control of breathing during oxygen deficiency at rest. *Acta physiol. Scandinav.*, (suppl. 38), 12: 1, 1946.
- MOTLEY, H. L. The use of oxygen in comatose states. *Bull. New York Acad. Med.*, 26: 479, 1950.
- BALDWIN, E. DEF., Cournand, A. and Richards, D. W., Jr. Pulmonary insufficiency. I. Physiological classification, clinical methods of analysis, standard values in normal subjects. *Medicine*, 27: 243, 1948.
- MOTLEY, H. L., Cournand, A., WERKO, L., HIM-

- MELSTEIN, A. and DRESDALE, D. The influence of short periods of induced anoxia upon pulmonary arterial pressure in man. *Am. J. Physiol.*, 150: 315, 1947.
29. BALDWIN, E. DE F., HARDEN, K. A., GREENE, D. G., Cournand, A. and RICHARDS, D. W., JR. Pulmonary insufficiency. iv. A study of 16 cases of large pulmonary air cysts or bullae. *Medicine*, 29: 169, 1950.
30. FERRER, M. I., HARVEY, R. M., CATHCART, R. T., WEBSTER, C. A., RICHARDS, D. W., JR. and Cournand, A. Some effects of digoxin upon the heart and circulation in man. Digoxin in chronic cor pulmonale. *Circulation*, 1: 161, 1950.
31. HARVEY, R. M., FERRER, M. I., RICHARDS, D. W., JR. and Cournand, A. The influence of chronic pulmonary disease on the heart and circulation. *Am. J. Med.*, (in press).

Conference on Therapy

Management of Thyrotoxicosis

THESE are stenographic reports of conferences by the members of the Department of Pharmacology and of Medicine of Cornell University Medical College and New York Hospital, with collaboration of other departments and institutions. The questions and discussions involve participation by members of the staff of the college and hospital, students and visitors. A selected group of these conferences is published in an annual volume, *Cornell Conferences on Therapy*, by the Macmillan Company.

DR. EPHRAIM SHORR: The disclosure that thiouracil has the property of causing thyroid hyperplasia simultaneously with diminished thyroid activity provided the impetus to one of the most significant developments in the management of hyperthyroidism in the past decade. The entire problem of non-surgical treatment of hyperthyroidism has come under scrutiny with attention focussed not only on the potentialities of numerous thioureas but also on radioactive iodine for the cure of hyperthyroidism. The enlarged perspective affords the opportunity to consider from several points of view the relative merits of non-surgical and surgical treatment of Graves' disease. Dr. Trunnell of the Memorial Hospital and the Endocrine Clinic of the New York Hospital will open the discussion.

DR. JACK B. TRUNNELL: Thyrotoxicosis is a disordered state of metabolism, the cause of which is not known in most cases. There are a few types in which the causes are now known. I shall do little more than name them for, if the cause is known, the treatment is in most instances self-evident.

It is almost certainly a fact that the syndrome of thyrotoxicosis is usually caused by overproduction of thyroid hormones in the thyroid gland. Whether or not this overproduction is brought about by some physiologic aberration primarily in the thyroid gland, or indirectly by overproduction or underproduction in other endocrine glands, is a matter of conjecture. Some types of pituitary overactivity, chiefly acromegaly, are often associated with hyperthyroidism. The notion that the common

garden variety of hyperthyroidism may result from pituitary overactivity has few adherents and is sustained by negligible evidence. We occasionally encounter an individual whose hyperthyroidism comes from a bottle. The term thyrotoxicosis factitia is applied to it. It is not always easy to establish this diagnosis because, for some strange reason, some of these patients have a strong disinclination to reveal the fact that they have been taking a medication and direct interrogation often elicits only a firm denial. The administration of thyrotropic hormone may bring on hyperthyroidism. Another variety of hyperthyroidism is seen in patients with thyroid cancer and metastatic deposits. This is very rare. The majority of these show no evidence of hyperthyroidism, even cases with as much as 2 kg. of metastatic thyroid which has the appearance of functioning tissue on morphologic examination. In these cases transient hyperthyroidism may result from the thyroid hormone entering the circulation during the breakdown of thyroid cancer in which hormone has been produced and stored.

I shall now outline briefly the various methods of treatment of hyperthyroidism. The order in which I will refer to them is not that of their relative importance. Iodine plays a role in the various phases of the treatment of Graves' disease, but its utility has several limitations. In some mild cases the use of iodine alone, in the form of potassium iodide, Lugol's solution or the syrup of hydriodic acid, may serve to control the hyperthyroid state for fairly long

periods but it is not an especially potent agent and, while it may lessen the symptoms, it often fails to bring the metabolic rate down to a normal level in severe cases. A more dependable application of iodine is its use for producing a remission in preparation for thyroidectomy. It has the advantage of being simple to administer, is inexpensive and is usually not toxic, although there are some who exhibit specific hypersensitivity to iodine. Escape from the action of iodine represents one of the disadvantages of its use both in the long-term treatment of hyperthyroidism and in its more intensive application preparatory for operation. How iodine produces its effects is the subject of controversy. According to one view it blocks the stimulating action of the thyrotropic hormone. It may do this either in the gland at the site where the thyrotropic hormone functions (as suggested by the work of Rawson) or elsewhere.

The surgical treatment might be mentioned next. There is little obscurity or controversy in regard to the mechanism by which surgery brings about results. There is some indication that lymphoid or muscle tissue gives rise to substances with calorigenic properties peculiar to the thyroid hormone but, even if they do, the amounts are insufficient to produce hyperthyroidism. The mechanism of action of thyroidectomy is simply the removal of the only tissue in the body with a well defined capacity to produce calorigenic substances. The rapid cure by a single procedure, as by the removal of a part of the thyroid, is an obvious advantage. There are, of course, disadvantages in surgery. There is the operative risk, but this has become very small because the means by which patients are prepared for surgery are effective and these have almost eliminated the old bugaboo of the thyroid storm. The possibility of myxedema after the operation is a disadvantage although this complication may be successfully managed. The production of hypoparathyroidism with attendant tetany is a fairly serious hazard; and although there are medical measures for

treating it, this complication is certainly not a pleasant one. Injury or severance of the recurrent laryngeal nerve producing paralysis of the vocal cord with resulting impairment of speech and laryngeal obstruction is also a rather serious complication but in this the skill of the surgeon plays an important part.

The first non-surgical measure, after ordinary iodine, which achieved any conspicuous degree of popularity was the use of the derivatives of thiourea. These compounds prevent the thyroid from synthesizing its hormone. They are supposed to do this by inactivating a peroxidase enzyme the normal function of which is oxidation of iodide to iodine. Tyrosine cannot combine with the iodide ion. For this elemental iodine is required; so if the thioureas prevent the production of iodine; they also prevent the synthesis of thyroid hormone.

The indications for the use of thiouracil are becoming more and more clear-cut. Some individuals obtain a permanent cure after varying periods of treatment with thiouracil or propylthiouracil. It would seem that all patients should receive a trial of this agent, but from a practical standpoint it is well to apply it to certain kinds of patients only, namely, those who can be relied upon to take the medicine regularly and to adhere to a plan for regular testing of the white blood cell count and for frequent measuring of their thyroid activity. In the patient in whom thiouracil as a permanent treatment is not feasible, it serves very well as a means to prepare the patient for thyroidectomy. Given together with iodine, thiouracil provides a measure that is unsurpassed for correcting the metabolic state prior to operation.

These compounds are not free of toxicity. There is the rare instance of fatal agranulocytosis. Death from renal failure occurs occasionally. This is rare and may be prevented by proper supervision. Unfortunately, the close supervision that is necessary for this purpose requires a degree of cooperation from the patient which is not easy to secure. Another practical

problem arises from the fact that these compounds lead to hyperplasia of the gland and hypervascularity, providing the surgeon with a gland that is friable, hemorrhagic, sometimes ill-defined, and hard to manage. It is a source of real difficulty which can, however, be controlled by the routine administration of iodine in the form of Lugol's solution or syrup of hydriodic acid for about ten days to two weeks before the operation. The iodine prevents the thyrotropic hormone from stimulating the thyroid cells to hyperplasia while the thiouracil continues to suppress the synthesis of the thyroid hormone.

The use of x-ray to destroy the thyroid gland in the treatment of hyperthyroidism was fairly popular at one time but is now much less so. It was chiefly applicable to patients who could not tolerate surgery, such as the poor surgical risks by reason of heart disease, or to patients with recurrences after several surgical attempts to remove the tissue. The main disadvantage of treatment with x-ray is the fact that other tissues are exposed to heavy radiation in an endeavor to apply enough to the thyroid gland to suppress the formation of the hormone.

X-ray has been largely replaced by radioactive iodine as one of the most recent therapeutic tools. It destroys thyroid tissue in much the same way as the x-ray. It has the advantage that adjacent tissues do not receive nearly as much radiation as the thyroid itself. Its administration is easy. Often one dose is adequate if the calculations are properly made. It is superior to other non-surgical management of hyperthyroidism, especially in those patients who for one reason or another fail to adhere to the regular schedule of visits and tests necessary to avoid treatment that is either too little or too much. Radioactive iodine is indicated in the rare cases of hyperthyroidism which occur in metastatic thyroid cancer, where the circumstances preclude operation and x-radiation. Thiouracil and its related compounds sometimes control the hyperthyroidism in these cases but we

have evidence which indicates that the production of thyroid hormone by functional thyroid cancer differs in some respects from that of the hyperplastic gland of Graves' disease, and that the response to thiouracil is not as satisfactory as one might expect.

I should like to say a few words on the subject of how to use radioactive iodine. I hope that my spending more time discussing this therapy will not be taken to signify that it is a superior method of treatment. I do not think it is. It has serious defects at the present time. The ideal treatment has not yet been discovered. Perhaps the closest to the ideal in the present stage of our knowledge is subtotal thyroidectomy.

If it is decided to treat with radioactive iodine, the patient first receives a very small tracer or test dose of the order of 25 to 50 microcuries, the amount depending on the sensitivity of the Geiger counter which happens to be available. This step serves two very important purposes: First, it helps establish the diagnosis in some of the very obscure cases or to verify the diagnosis made in other ways; second, by means of this preliminary test it is possible to determine how much of any dose of iodine the particular thyroid gland may be expected to collect and how long the iodine is retained. The amount of the iodine lost in the urine provides information concerning these factors. One then calculates, or what is really the case, estimates the size of the thyroid gland which is to be treated. From these data the dosage of radioactive iodine is determined. This procedure calls for more art than science. In estimating the size of the thyroid gland the tendency is to describe it as smaller than it is, rarely the reverse. It has been found, largely through the method of trial and error, that 150 microcuries of radioactive I^{131} per gm. of estimated thyroid weight will yield the highest percentage of satisfactory results. The necessity for a second dose indicates that too little radiation was delivered, and the production of myxedema signifies that the amount of radiation was excessive. If the

estimated dose is conspicuously less than 150 microcuries, a fairly large proportion of the patients will require additional treatment. On the other hand, if one uses much more than 150 microcuries, the incidence of myxedema will be unnecessarily high.

The therapeutic results of treatment with radioactive iodine are not manifest immediately. The delay constitutes a serious disadvantage of this therapy in patients in whom thyrotoxicosis has brought about impairment of the heart and circulation.

The treatment of the eye changes of Graves' disease is highly controversial. There are some who believe that the use of radioactive iodine is safer than surgery in cases with advanced eye changes for the reason that with radioactive iodine the cessation of hormone production is more gradual and is, therefore, less likely to result in exacerbation of serious eye signs. I do not believe there is enough evidence on this point one way or the other. The management of advanced exophthalmus is often a medical emergency, particularly if the condition grows rapidly worse as it often does without warning. It calls for the skill of an expert eye specialist; but if one is not available, it is wise to try a measure which has given some evidence of value, namely, dehydration through a salt-restricted diet and mercurial diuretics. To have the patient sleep with the head in an elevated position is of some advantage because it facilitates drainage of excess fluid from the orbital area. Radiation of the orbital tissues has been suggested, but there are no recent experiences to support this measure. Some workers in the field of thyroid disease consider thyroid hormone of value, others regard it as useless. I have had little personal experience with it and in those in whom I have observed the use of thyroid in exophthalmus I have not been impressed by the results.

Other special features present themselves in the general management of hyperthyroidism. There are the cases of cardiac failure associated with thyrotoxicosis. As a rule they do not respond to digitalis as well

as do patients with heart failure on the basis of other etiology. The most important single therapeutic measure in such cases is the endeavor without delay to control overproduction of the thyroid hormone. Then there is the problem of nutrition in patients rendered cachectic by long-neglected Graves' disease. These patients need large amounts of protein, carbohydrate and vitamin supplements.

DR. SHORR: Dr. Eckel, may we now hear from you, as a surgeon, how matters stand in the treatment of hyperthyroidism?

DR. JOHN ECKEL: From the standpoint of the surgeon the strides in the treatment of thyroid disease have been tremendous in the past five or six years. It is not the operative technic which has improved particularly, if at all. If we compare results in the past five years with those in the five-year period just preceding, we find no substantial difference in the frequency with which recurrent laryngeal nerves have been injured or severed, and the incidence of hypoparathyroidism resulting from the operation has not changed appreciably.

The advances have been made in several directions. First, there is the improvement in the method of preparing the patient for operation. The use of thiouracil or propylthiouracil and iodine for this purpose represents a remarkable advance. Prior to this period, only iodine was available to establish remission preparatory to operation. The response of many patients to hydriodic acid or Lugol's solution was very slow. The result was prolonged periods of hospitalization. Many patients failed to show any response so that the operation had to be postponed almost indefinitely. During these long periods of waiting the surgeon and internist were in almost daily conference in order to spot the day which seemed optimum for the operative procedure. Even so, postoperative thyroid storm was not infrequent, and many of these patients died. Since the use of thiouracil or propylthiouracil for preparation I have not seen a single thyroid storm following the operation.

It is no longer necessary, in most in-

stances, to have the patient in the hospital for periods of weeks to months, as used to be the case, to prepare for the surgical procedure. It is now our usual practice to pursue the patient's course through visits to the clinic or the office until the signs of hyperthyroidism subside and remission from the use of thiouracil or propylthiouracil, together with iodine, is established. The patient is then admitted to the hospital a few days prior to the date which is set for the operation.

Dr. Trunnell has already referred to the need for iodine. With propylthiouracil alone the operator is confronted with a gland which is exceedingly vascular and friable, and the operative procedure may be complicated by active bleeding. When an adequate amount of iodine is used in the preoperative period, the gland is apt to be firm, easily delivered and is not likely to present undue bleeding when the clamps are placed. The belief that propylthiouracil has made the surgical procedure more difficult does not coincide with my experience when iodine is also used for an adequate period and in adequate dosage.

Prior to the period of this type of preoperative preparation the two-stage operation was performed from time to time. These were the cases in which the operation had to be abandoned after a lobectomy and then completed about ten days later. This was made necessary by the appearance of threatening signs. During the operation not infrequently the pulse rate rose and reached very high levels. This dangerous state was considered to be due to the liberation of thyroid hormone. The anesthetist would often become alarmed and it was considered wise to interrupt the operation. Since the use of propylthiouracil I have not had to do this, and I believe that none of us who operates here has been forced to perform the two-stage operation.

There are several other serious problems in hyperthyroidism which have been partly or wholly solved by the developments of the past few years. A radical change has taken place in the treatment and outlook for so-

called juvenile goiter. This type of toxic goiter always presented serious difficulties. Up to as recently as five or six years ago we were forced to operate on many children. The results were almost uniformly poor. Most of the juvenile group were admitted to the hospital and observed for protracted periods, sometimes months, before the operation. The operative procedure was hazardous. Thyroid storm was frequent. The death rate was relatively high. Recurrence of hyperthyroidism following discharge from hospital was common. Since working in the Endocrine Clinic here I have been greatly impressed with the remarkable results produced by propylthiouracil in children who take the treatment while they continue their work at school. We have not operated on a single juvenile goiter.

The juvenile group and the elderly persons with advanced cardiac disease made up the bulk of high-risk cases. They headed the list of mortalities. With the new preoperative preparation the hazards of thyroidectomy have markedly decreased. Our mortality rate has become negligible, partly because high-risk cases such as those I have just mentioned are less prone to come to surgery. Many of them have been managed successfully with propylthiouracil, and now with radioactive iodine.

Carcinoma of the thyroid may also be included among the problems aided by recent surgical advances. The diagnosis of carcinoma of the thyroid gland is made much more frequently in the past ten years than previously. In the past we were inclined to carry out minimal procedures in these cases. It is now the practice to perform total thyroidectomy, and many surgeons advocate radical neck dissection on the side where the tumor was removed. If careful microscopic examination shows carcinoma in the other lobe, bilateral radical neck dissection should be performed. Dr. Trunnell has mentioned the use of radioactive iodine in conjunction with surgery.

In connection with the more frequent diagnosis of carcinoma of the thyroid and the more extensive procedures in treatment

there are still some unanswered questions. We frequently remove what we believe to be a non-toxic adenoma and then the pathologist reports a carcinoma. We thus find ourselves in the unpleasant position of having performed only a minimal operative procedure on what was considered to be a carcinoma. We have to give some thought to the question whether carcinoma of the thyroid has really become more frequent, or whether we are finding more of them because we search more carefully, or whether we name more tumors carcinoma by reason of a change in pathologic criteria.

DR. HARRY GOLD: Is it proper to assume that what happens to the patient with Graves' disease depends on whether he lands in the hands of an expert thyroid internist or an expert thyroid surgeon? Are the two likely to offer similar advice, or is the internist apt to attempt to bring the hyperthyroidism under control with propylthiouracil and maintain the results with this drug while the surgeon will proceed directly to utilize the propylthiouracil as a means of preparation for operation? I have encountered such differences in procedure depending on whether it was an internist or a surgeon the patient consulted.

DR. EUGENE COHEN: I should like, first, to say a word or two about the drugs employed in the management of hyperthyroidism. During the conference reference was frequently made to thiouracil with the implication that this compound and propylthiouracil are interchangeable. This is not the case. The propyl compound is much less toxic. Thiouracil is responsible for several instances of fatal agranulocytosis.

In regard to Dr. Gold's question, I would say that about 80 per cent of the hyperthyroid patients whom I see eventually go to the surgeon. I believe that Dr. Shorr holds that the number who end up as surgical problems is smaller, about 60 per cent.

DR. GOLD: That is not quite an answer to my question. Does the surgeon advocate a trial of propylthiouracil as a definitive form of treatment in the conventional case of Graves' disease, or is his use of the drug

from the very start only a measure to prepare the patient for operation?

DR. ECKEL: I will answer that question by saying that the surgeon should make a trial of propylthiouracil first.

DR. GOLD: I take it, then, that you believe there are enough cases of Graves' disease in which propylthiouracil produces a lasting cure to justify the medical trial first. If the trial proves unsuccessful, you turn to operation; if, on the contrary, it does prove successful, the surgeon continues or should continue the medical treatment, or possibly turn the patient over to an internist who may have more time for such things.

DR. SHORR: I perceive a drift toward a rigid position in the treatment of Graves' disease. The history of this disease should warn us that we are probably far from the end of the chapter. It is too early to adopt any routine method exclusively. There are always a few cases that fail to respond to one or another method. There are recurrences after surgery. There are failures with radioactive iodine. There are also failures with propylthiouracil. In view of this state, continued investigation is imperative and one cannot emphasize too strongly the need for individualizing treatment.

DR. GOLD: How do you account for the fact that four of five patients who are given a trial of propylthiouracil therapy eventually come to surgery? Is it a case of only about 20 per cent of the patients being sufficiently sensitive to the drug, the remainder either acquiring tolerance or from the very beginning failing to respond no matter how much of the drug is given or how long the administration is continued?

DR. COHEN: Almost all patients with Graves' disease respond to propylthiouracil. The reason we turn to surgery so often is the difficulty in maintaining the results satisfactorily over long periods of time. I might mention a few of the complicating factors. The thyroid gland may become enlarged and may cause pressure symptoms. The degree of control of Graves' disease by means of the drug is often inconstant, and if the heart is involved troublesome symp-

toms may appear. Inconstant control of the hyperthyroidism may be due to the patient's failure to take the medication regularly. The drug is sometimes discontinued during infection. If the patient travels, the basal metabolism and blood cholesterol tests as guides to dosage are often neglected. In cases which we have observed for periods of six or seven years we have found that the required dosage varies considerably, both from patient to patient and in the same patient at different times. Some have required 200 or 300 mg. of propylthiouracil daily during the entire period while in others it was found necessary to reduce the early large doses to 75 or 50 mg. daily for maintenance. In these continued use of the larger doses would lead to hypothyroidism. When the drug is used for protracted periods, temporary factors appear which diminish the efficacy of the small doses, giving rise to periods of Graves' disease. Because of these problems, and of the fact that surgical complications are so few in large medical centers, we ultimately refer the major proportion of our patients for surgical operation.

DR. GOLD: That has been my experience also. A satisfactory remission is easily induced by propylthiouracil but to maintain it is another matter. Something seems to be forever happening to upset the smooth course. Unexpectedly, the basal metabolic rate is found to have risen too high, or to have fallen too low; weakness appears in association with myxedema; pounding of the heart and rapid heart rate reappear in relation to the basal metabolic rate that has gone up. In order to avoid the need for frequent tests I have tried the plan of urging patients to keep a closer eye on symptoms which might serve as a guide to change in dosage before the situation is too far out of hand. While this is sometimes helpful it is not always so. There are cases in which such preoccupation with symptoms results in hypochondriasis. Confusion arises from symptoms which may bear no relation to the condition of the thyroid. The patient in whom propylthiouracil is used as a defini-

tive therapy in Graves' disease sometimes shows a striking change in attitude as the treatment is continued. At the start the prospect of escaping an operation through the simple device of oral medication is warmly embraced but it is not long before the operation with its outlook for a more stable state of health becomes a welcome suggestion for relief from the unpleasant position of worry and apprehension.

DR. SHORR: How high is the mortality rate from the operation in a large center such as this, and how high is it in the country as a whole?

DR. ECKEL: I cannot say exactly but I have no doubt that the mortality following operation in large centers like this one is practically nil at the present time.

DR. WALTER MODELL: In the case of treatment with radioactive iodine is there any harm in the prior use of propylthiouracil or iodine?

DR. TRUNNELL: Yes, there is. Iodine in any form, even that painted on the skin or taken as a dye for x-ray of the gallbladder, may make it necessary to postpone radioactive iodine therapy for periods ranging from three weeks to a year.

DR. GOLD: While we are on this subject I should like to restate the problem of radioactive iodine therapy. It is the objective of its use in hyperthyroidism to secure in the gland a quantity of radiation sufficient to destroy a proportion of overfunctioning follicles. The problem of accumulating the isotope in the gland involves the experimental observation that a minute dose of iodine given to a person with hyperthyroidism will be fixed almost entirely in the thyroid, the quantitative aspects being something like this: After an oral dose of less than 2 mg. of iodine given to a patient with Graves' disease, about 75 or 80 per cent accumulates in the gland in a few hours. How fast the gland gives up this iodine is another factor which determines the total effect of a particular dose. The iodine uptake by the gland and the duration of its fixation there, as judged by urinary excretion of iodine, are two of the tests

employed to estimate the dose for a particular patient in order to avoid failure of therapy from too little radiation or myxedema from too much. The objection to the prior use of propylthiouracil and iodine is due then to the fact that they invalidate the results of the tests in one or another way. For example, the value for excretion may be too high if there is an overabundance of iodine, for then the body reacts by greater excretion; the value for uptake may be too low if there is abundant iodine in the gland, as under normal conditions, for then the gland takes up only a small part of a dose; similarly for the level of blood iodine which, if high, will result in a low uptake by the gland.

DR. FRIEDRICH GUDERNATSCH: After a dose of radioactive iodine, a considerable amount of the material passes into tissues other than the thyroid gland. Are there any facts regarding possible damage by the radiation outside of the thyroid?

DR. TRUNNELL: Your question is an important one. We are preparing a report for the American Goiter Society on a study of the concentration of radioactive iodine in every tissue of nine patients who died within 24 to 120 hours after a dose of radioactive iodine. When the dose of radioactive iodine is large, as in the treatment of cancer, the danger to other tissues has to be taken into consideration, but the amount given in hyperthyroidism is relatively small and presents no serious hazard to other tissues.

DR. SHORR: I presume that includes the pituitary also.

DR. TRUNNELL: The present method of measurement shows that the concentration in tissues is much lower than that shown by the values reported a few years ago. The data summarized in Salter's book on the subject will, I think, have to be revised downward by a large factor.

DR. GOLD: How much total iodine is there in the "cocktail" of radioactive iodine which the patient takes?

DR. TRUNNELL: The two are synonymous. The material we use is carrier-free. It is all radioactive. The amount of iodine is very

small. A measurement made before the drought showed more iodine in New York City water than in a glass of similar size containing the largest therapeutic dose we have ever given, even for cancer. For radioactive I^{131} , a dose of 100 millicuries weighs only 0.08 gamma or 0.00008 mg. Since the average dose for hyperthyroidism is not to exceed 10 millicuries, the weight of the iodine given in the therapeutic dose is only 0.008 gamma or 0.000008 mg.

DR. GOLD: Is all that taken up by the thyroid gland?

DR. TRUNNELL: In any case which merits treatment of hyperthyroidism the amount collected by the gland should equal at least 50 per cent of the dose.

DR. SHORR: It sounds a little like homeopathy to me.

DR. GUDERNATSCH: Since the introduction of iodine for the treatment of hyperthyroidism by Plummer of the Mayo Clinic about thirty years ago, various explanations of the mode of action have been proposed. Could we have a few words on the current views concerning the mode of action?

DR. TRUNNELL: I might first state that the synthesis of thyroid hormone by the thyroid gland is under the influence of the thyrotrophic hormone of the anterior pituitary gland, which is in turn controlled to some extent by the hypothalamus. These facts are fairly well established but it is uncertain whether the primary control is exercised through a nervous mechanism or through another as yet unknown substance. The chief ingredients of the thyroid hormone are iodine and tyrosine. All the chemical steps in the elaboration of the final hormone are not yet established. As for the action of iodine in hyperthyroidism, several sites have been considered. There is the view that iodine inactivates the thyrotrophic hormone. Rawson has presented strong evidence to the effect that iodine prevents the thyroid gland from responding to the thyrotrophic hormone. There is still another formulation based on the observation that a rise in the level of serum iodine beyond a particular point decreases the

accumulation of iodine by the thyroid gland, and the rate of hormone synthesis is depressed by a high level of iodine. It is possible that all of these mechanisms may participate in the control of Graves' disease by the administration of iodine. It is also possible that there are other factors which have not yet been discovered.

DR. SHORR: In closing, I should like to emphasize the need for continued study of this disease, to point out that a great deal may be learned from the application of all the various procedures, and that much may be lost by confining the management of Graves' disease to any one therapeutic regimen which may at the moment seem superior, simple to apply, and which may make little demand on the physician in the long term care of the hyperthyroid patient.

SUMMARY

DR. GOLD: The conference this afternoon leaves us with little doubt that while we do not yet have the last word on the treatment of thyrotoxicosis, substantial advances have been made in the past few years. Surgical removal of the thyroid gland still remains the major therapeutic measure in the vast majority of patients with the conventional type of Graves' disease but the success of the operation depends to a large degree on the quality of the preoperative preparation. Up to but a few years ago this attempt at preparation involved several weeks or even months of hospitalization, the administration of iodine, and anxious waiting for the day when a remission would be sufficiently

advanced to reduce the hazard of surgical intervention. Even then, failures to secure satisfactory remission were numerous and postoperative thyroid storms were frequent. The use of propylthiouracil together with iodine has materially changed the outlook. With these measures adequate preoperative preparation is more rapid, more certain and more complete. It can be carried out with the patient in the ambulant state. Admission to the hospital may be postponed up to a few days prior to the date set for the operation. Postoperative thyroid storms have practically vanished. In centers best equipped for the management of Graves' disease mortality from thyroidectomy has virtually disappeared.

Several other measures in the therapy of Graves' disease were explored in this conference: the trial of propylthiouracil as a definitive form of treatment; the reasons for its failure in the majority of cases; its particular utility in juvenile goiter; the role of x-ray therapy; the place of treatment with radioactive iodine and the principles involved in its application.

In view of the common experience that highly effective new therapeutic measures are sometimes prone to retard the search for mechanisms in disease, a few warnings were issued, namely, the danger of confining treatment to one or another simple routine, the importance of continued study of the psychodynamics of Graves' disease, and the need for utilizing every opportunity provided by the prolonged care of these patients to secure insight into the basic factors involved in the process of the disorder.

Clinico-pathologic Conference

Recurrent Syncope

STENOGRAPHIC reports, edited by Robert J. Glaser, M.D., and David E. Smith, M.D., of weekly clinico-pathologic conferences held in the Barnes Hospital, are published in each issue of the Journal. These conferences are participated in jointly by members of the Departments of Internal Medicine and Pathology of the Washington University School of Medicine and by Junior and Senior medical students.

THE patient, F. W. (No. 188847), was a seventy-seven year old white housewife who entered the Barnes Hospital on September 11, 1950, because of loss of consciousness. The family history was of interest in that the patient's father and one aunt had both died of "strokes." The patient herself had enjoyed good health until the age of sixty-two when she passed several kidney stones. For several years prior to entry she had had "indigestion," which was characterized by epigastric burning and by eructation; neither was related to meals and both were promptly relieved by tablets of an unknown type. Urgency and frequency of urination, present for a number of years, had become more marked in the six weeks prior to entry.

About eight years before admission the patient's blood pressure was found to be elevated. Subsequently, she had episodes of irregular heart action and palpitation for which she was given digitalis; because of vomiting, however, she discontinued taking the drug. Her physician then prescribed a second drug which produced reversion to a normal rhythm. Although she had had slight dyspnea on exertion, she had never had signs of frank cardiac failure nor had she experienced chest pain. During the several years prior to entry the patient developed a shuffling gait with rapid steps, and in the two or three months before admission she had fallen on several occasions; the falls were not preceded by vertigo or by loss of consciousness. Sixteen hours before entry while sitting in church she suddenly slumped over. Although she was unable to speak, she stated subsequently that she had been able to hear those about her. One hour later she was able to respond although her speech was thick, and she developed fecal and urinary incontinence. No other abnormal signs appeared. Four to five hours after the syncopal attack she was able to walk to the bathroom.

She was referred to the hospital for study and care.

At the time of admission physical examination revealed the temperature to be 37°C., pulse 80, respirations 20 and blood pressure 200/120. The patient was moderately obese and did not appear ill. Her speech was somewhat slow and she was not completely oriented. No cyanosis was noted. The pupils reacted well to light and accommodation and aside from slightly narrowed arterioles the fundi appeared normal. Examination of the upper respiratory tract was negative. The patient exhibited slight postural emphysema but the lungs were clear to percussion and auscultation. The heart was slightly enlarged to the left; the rhythm was irregular and the sounds were of poor quality. A₂ was greater than P₂. A short grade II systolic murmur was heard at the apex. Abdominal examination was negative. There was no peripheral edema and the arterial pulses in the legs were equal and full. Aside from the speech defect no abnormal neurologic findings were noted.

The laboratory data were as follows: *Blood count*: red cells, 4,300,000; hemoglobin, 13.2 gm.; white cells, 10,700, with 6 stab and 78 segmented forms. *Urinalysis*: negative. *Stool examination*: guaiac negative. *Blood Kahn test*: negative. *Blood chemistry*: non-protein nitrogen, 18 mg. per cent; sugar, 73 mg. per cent; cholesterol, 248 mg. per cent. *Basal metabolic rate*: plus 6. *Roentgenogram of the chest*: The trachea was displaced to the left. There was a curvilinear shadow extending from the superior right cardiac border along the paravertebral region into the area within the circle of the first rib on the right. This shadow was not definitely visualized on the lateral view. It was thought to have an appearance consistent with either an aneurysmal dilatation of the innominate artery or with thyroid enlargement. Cardiac enlarge-

ment was noted, primarily left ventricular in origin. Rather extensive calcification was visualized in the arch and descending portion of the thoracic aorta. The lung fields were essentially clear. *Electrocardiogram*: T waves were inverted in AVL, upright in V1; there was counterclockwise rotation of the heart.

The patient was seen soon after entry by a neurologic consultant who described no abnormal signs other than the arteriolar changes in the fundi and some generalized muscle rigidity. Artane, 2 mg. four times a day, was prescribed. On the second day the patient developed nausea and the dose was cut in half. She was occasionally disoriented but otherwise her condition was satisfactory. Her blood pressure remained elevated and on the fifth hospital day it was 180/110. A glucose tolerance test was essentially normal.

During the second week of hospitalization the patient was less confused mentally and her speech became more distinct. Her blood pressure was 140/85. She was able to sit up in a chair and, aside from epigastric fullness about one-half hour after meals, she felt quite well. At this time skull x-rays were obtained and revealed only minimal hyperostosis frontalis interna. The patient was up progressively and her blood pressure remained at levels of about 150/90.

At the end of her third hospital week a gastrointestinal x-ray series was performed. The esophagus appeared within normal limits in its upper portions. Approximately 10 cm. above its diaphragmatic portion there was rather sharp deviation to the left with return of the diaphragmatic portion to the normal position. There was also very slight anterior displacement. The esophageal walls were smooth and there was no evidence of intrinsic disease. No explanation was advanced for the displacement. The only other finding was diverticulosis of the colon. During the course of the gastrointestinal examination the patient became momentarily unconscious on one occasion, but otherwise she continued to feel quite well.

Approximately one month after entry she developed slight pain at the right costal margin. Complete examination showed no changes from the previous findings. Two days later she apparently fainted momentarily while sitting in a chair. She was nauseated at the time and complained of epigastric discomfort without severe pain. She then became incontinent of feces. When examined her pulse was found to be 120

and regular, the blood pressure 132/98. The heart sounds were of good quality and no other abnormalities were apparent. Blood taken at the time of this episode revealed the non-protein nitrogen to be 20 mg. per cent and the blood sugar 116 mg. per cent. X-ray films of the esophagus were repeated and found to be the same as on the first examination. An electrocardiogram revealed elevated S-T segments in V3 and AVF, auricular premature contractions and horizontal position of the heart with clockwise rotation.

The patient continued to have mild but rather persistent nausea. About one week before death her white blood count rose to 14,700 with a differential showing 6 stab and 69 segmented forms. The patient was afebrile at this time and the urinalysis was negative. A lumbar puncture was performed, revealing an initial pressure of 145 mm. of water and a final pressure of 110 mm. of water. The fluid was clear and contained only one lymphocyte. The protein was 38 mg. per cent, sugar 70 mg. per cent, and the colloidal gold curve was flat. The Wassermann test was negative. The patient's nausea gradually subsided and aside from some pain in the right upper quadrant she felt quite comfortable, was rather alert and was sitting up a good bit of each day.

On October 18, 1950, approximately five weeks after entry, the patient had sudden severe pain in the middle of her back which radiated to the right costal margin. When she was examined shortly after its onset, the cardiac rhythm was found to be grossly irregular with a rate of 104; the radial pulse was thready. Her blood pressure was unobtainable and her respirations were short and gasping. Despite emergency measures the patient died thirty minutes after the onset of the pain.

CLINICAL DISCUSSION

DR. HARRY L. ALEXANDER: This elderly woman had mild hypertension and arteriosclerosis. She had enjoyed good health, however, until the onset of syncopal attacks. Prior to her first attack, which occurred while she was in church, she had had only vague gait disturbances. It would be helpful if we could determine the nature of the lesion which produced the first episode. Dr. Levy, would you suggest its possible cause.

DR. IRWIN LEVY: As near as can be determined from the history, the patient merely

slumped over at the time of her first attack. One assumes therefore that no convulsive manifestations appeared at that time. Subsequently she had a moderate residual speech disturbance; on the basis of those facts one would suspect a vascular lesion, either thrombotic or embolic in origin.

DR. ALEXANDER: Does the fact that she was incontinent have particular significance?

DR. LEVY: No. It merely suggests residual clouding of the sensorium.

DR. ALEXANDER: I gather that you believe an occlusive vascular lesion is a more probable explanation of the attack than hemorrhage?

DR. LEVY: Yes, I think so.

DR. ALEXANDER: Does the fact that the episode was sudden in onset favor thrombosis?

DR. LEVY: It is consistent with either thrombosis or embolus.

DR. ALEXANDER: Is there any validity to the concept of angiospasm?

DR. LEVY: Yes, I think there is. We certainly see patients with transient cerebral phenomena which promptly clear. They may occur repeatedly without residual manifestations and it is reasonable to assume that there may be a transient disturbance in blood supply to explain the transient disturbance in function.

DR. ALEXANDER: Does the fact that this patient apparently had residual manifestations for a definite period following her first episode rule out angiospasm as the etiologic factor in this case?

DR. LEVY: Yes. It would not explain persistent abnormalities such as this patient exhibited.

DR. ALEXANDER: Subsequent to her first episode the patient had a number of syncopal attacks, all of which were rather transient in nature. A lumbar puncture performed several weeks after her entry into the hospital was negative. Do those results help in reaching a diagnosis?

DR. LEVY: The negative lumbar puncture tends to rule out hemorrhage of significant degree, but is otherwise not particularly helpful. It should be noted that repeated syncopal attacks are not commonly seen with either thrombosis or embolism.

DR. ALBERT I. MENDELOFF: Is it not conceivable that this woman had the carotid sinus syndrome. In this age group repeated episodes, particularly when the patient was sitting up, suggest that possibility.

DR. LEVY: It certainly should be considered. One would have to assume, of course, that at least one of the episodes resulted in residual cerebral damage.

DR. MENDELOFF: Could not cerebral damage occur if the attack lasted several minutes?

DR. LEVY: I think so.

DR. EDWARD MASSIE: One should also consider complete heart block. What has been said about carotid sinus syncope can certainly apply to complete block also.

DR. ALEXANDER: That is a good suggestion.

DR. W. BARRY WOOD, JR.: I was impressed by the fact that this patient had multiple attacks, and as Dr. Levy has indicated, multiple attacks of syncope are rather unusual in ordinary cerebral thrombosis; it suggests possibilities other than vascular disease of the brain. For example, aortic stenosis is a common cause of recurrent syncope. Similarly, in dissecting aneurysm of the aorta if the arterial trunks to the brain are involved, a similar sequence may occur. In a recent article Moersch and Sayre discuss the neurologic complications of dissecting aneurysm; 46 per cent of the patients in their series had various neurologic manifestations.* Some developed hemiplegia, others transverse myelitis, and several had repeated attacks of syncope without residual manifestations. I suggest, therefore, as a possible diagnosis in this case, dissecting aneurysm of the aorta.

DR. ALEXANDER: Dr. Harting, would you like to make any comments on the x-ray findings?

DR. HUGH R. HARTING: Calcification and tortuosity of the aorta were marked. As indicated in the protocol, there was a curvilinear shadow in the region of the innominate artery which was thought by our department to represent a possible aneurysm or dilatation of the innominate artery. Such a diagnosis is rather uncertain. We have seen similar findings in patients who at autopsy showed no abnormalities of the innominate artery. Similarly, the deviation of the esophagus which was described in the protocol may or may not have been significant. Frequently in elderly people similar changes are seen in the absence of any demonstrable lesion.

DR. MENDELOFF: I would agree with Dr. Harting that frequently in old people the esophagus may appear grossly distorted in its

* MOERSCH, F. P. and SAYRE, G. P. Neurologic manifestations associated with dissecting aortic aneurysm. *J. A. M. A.*, 144: 1141, 1950.

course and yet may actually at autopsy be perfectly normal. It may be fixed to a markedly calcified aorta.

DR. ROBERT A. MOORE: It should be mentioned that the fact the pathologist does not demonstrate abnormal deviation or abnormal position of a given thoracic structure does not mean that such a deviation was not present in life. When the thorax is opened, the pressure relationships are markedly altered, and there are obvious reasons why moderate changes in position present in life may not be demonstrable at autopsy.

DR. ALEXANDER: The possibility that the shadow in the upper mediastinum represented an enlarged thyroid was put forth. If that were true, should the gland not have been palpable, Dr. Daughaday?

DR. WILLIAM H. DAUGHADAY: No, I do not think so. Thyroid tissue commonly occurs in the mediastinum, and in such cases is completely separate from the thyroid gland itself.

DR. ALEXANDER: If this patient had had an innominate aneurysm, should not one have seen a pulsation? Are not innominate aneurysms usually palpable?

DR. MASSIE: Frequently they are.

DR. WOOD: That would depend somewhat on whether or not a clot was present on the wall of the aneurysm. An aortic aneurysm sometimes does not pulsate when it contains a large clot in its lumen.

DR. HAROLD SCHEFF: Dr. Alexander, the anterior displacement of the esophagus which was described could have been due to an aneurysm of the descending aorta which impinged on the esophagus.

DR. ALEXANDER: It certainly seems conceivable that the entire clinical picture could be explained on the basis of that diagnosis. The terminal episode also was consistent with the diagnosis of dissecting aneurysm in that the patient had sudden, severe pain in the back which radiated to the right upper quadrant. Are there any other suggestions?

DR. JOSEPH C. EDWARDS: If the patient had an aneurysm, a tracheal tug should have been demonstrable.

DR. WOOD: A tracheal tug may be difficult to demonstrate unless one is careful to move the trachea to either side of the midline. I am reminded of an occasion when Dr. Warfield T. Longcope demonstrated a striking tracheal tug in a patient with an aneurysm after having been

assured that the patient did not have a tug. Dr. Longcope merely moved the trachea to one side whereupon the tug was demonstrable.

DR. ALEXANDER: Returning to the terminal episode it should be recalled that this patient had rather mild gastrointestinal symptoms for some years. Dr. Scheff, do you believe that the terminal event may have arisen on the basis of some gastrointestinal lesion.

DR. SCHEFF: No, I do not. As I have indicated, I think that dissecting aneurysm is the most likely explanation of the entire illness.

DR. EDWARD MASSIE: I would like to suggest as a possibility, or indeed a probability, terminal pulmonary embolism. It should be recalled that at the time of entry the electrocardiogram showed counterclockwise rotation of the heart. This term has no anatomic connotation; it merely concerns the position of the heart in terms of the electric field. Approximately one month later, without apparent reason, the electrocardiogram showed clockwise rotation of the heart. Such a finding occurs in pulmonary strain or in pulmonary embolism and since the patient died about six days after the second electrocardiogram was obtained, pulmonary embolism must certainly be considered.

DR. ALEXANDER: Would you not have expected changes in the T waves under those circumstances?

DR. MASSIE: Certainly one would expect to see incomplete right bundle branch block and inverted T waves in Leads V1, V2 and V3; all of these deviations would indicate strain of the right ventricle, but one may see none of those and find only clockwise rotation.

DR. ALEXANDER: The pain was perfectly consistent with the diagnosis of massive pulmonary embolism, was it not? I should like to put forth also the possibility of a terminal myocardial infarction. Dr. Massie, do you think that diagnosis is tenable?

DR. MASSIE: It is always tenable in a situation such as this, but without further electrocardiograms one can only speculate.

DR. ALEXANDER: In summary it seems clear that the diagnosis of dissecting aneurysm of the aorta is favored, but Dr. Massie has also suggested the possibility of massive pulmonary embolism, and myocardial infarction has also been considered.

Clinical Diagnoses: Dissecting aneurysm of the aorta; ? pulmonary embolism; ? myocardial infarction.

PATHOLOGIC DISCUSSION

DR. J. D. WHEELER: Neither an aneurysm of the aorta or innominate artery, nor intrathoracic thyroid tissue were present in the superior mediastinum. Following removal of the thoracic organs no lateral deviation of the esophagus was apparent. Nothing that might have provided an anatomic basis for displacement of the esophagus was found either in the esophagus or in the mediastinum after the physiologic relationships had been destroyed by removal of the sternum. The right pulmonary artery and its primary branches contained a partially organized thrombus which occluded its lumen. The left main pulmonary artery was dilated, and there were mural thrombi on its wall. The tertiary branches of the left pulmonary artery in the lower lobe contained thrombi. One pyramidal focus of recent infarction, 2 cm. in width, was found at the periphery of both the right upper and the left lower lobes of the lungs.

The heart weighed 450 gm. with hypertrophy predominantly of the left ventricle. There was a partially organized thrombus which measured 5 mm. by 15 mm. in the apex of the right ventricle and the thebesian veins. The coronary arteries showed moderate arteriosclerosis but the lumens were patent. The liver and spleen were congested. The kidneys were of normal size and had finely granular surfaces with scattered broad-based scars. The renal and cerebral arteries showed moderate arteriosclerosis; the aorta exhibited advanced arteriosclerosis with calcification and some ulceration. Petechiae were found in the left inferior frontal gyrus of the brain, and there were areas of old encephalomalacia, 3 mm. in diameter, involving the right putamen, and 10 mm. by 15 mm. involving the left putamen and caudate nucleus.

DR. ROBERT A. MOORE: The predominate gross lesions were in the vascular system with other lesions of the heart, brain, kidneys and lungs that were significantly related to the changes in the vessels. The exact order in which various lesions, particularly the thrombi in the pulmonary arteries, developed was not obvious from gross examination; but the microscopic sections present some relative points which enable us to establish the chronology of most of these lesions. In Figure 1 the capsule of the adrenal shows an example of the markedly hypertrophic and thickened arterioles that were present throughout most of the organs of this

patient. In Figure 2 there is similar advanced thickening of a small artery in the kidney, yet not very much interstitial fibrosis, obliteration of glomeruli or other changes in the renal substance. These changes are associated with hypertrophy of the heart and indicate that this patient had hypertension for at least long enough to develop distinct anatomic changes in the vessels and hypertrophy of the overloaded myocardium.

Further evidence of chronic vascular disease is given by the lesions in the brain. Figure 3 is of a cystic focus of old encephalomalacia in the putamen. There is a dense layer of astrocytes about the cyst and complete removal of fat and other products of necrosis. A number of months must have elapsed between the time the vessels nourishing these foci were occluded and the slow reparative processes of the brain could reach this stage. Except for the cortical petechiae there were no lesions in the brain more acute than the one illustrated.

The thrombi in the pulmonary arteries show an interesting variation in age. In Figure 4 a branch of the pulmonary artery out in the substance of the right lung is shown; it contains a thrombus that is considerably organized by interlacing bands of young fibrous tissue. The defect in the arterial wall and the separation of the thrombus from the wall are artefacts. Such a thrombus must be in a vessel for some weeks or possibly a few months to reach this stage of organization. In contrast, in Figure 5 the thrombus in the right main pulmonary artery shows no organization and only slight dissolution of the erythrocytes and layers of fibrin and platelets to indicate an age of a few weeks at most. There are no significant changes in the intima or media of the main artery, but an adjacent small artery has a greatly thickened intima and a calcified plaque in the media. Figure 6 is of a section stained for elastic tissue in which there is a muscular artery that can be identified as a bronchial artery. Among the arteries several millimeters or more in diameter in the normal lung the pulmonary arteries are typical elastic arteries while the bronchial arteries are of the muscular type. In this particular field the edge of an elastic artery filled with organized thrombus lies in the upper left corner, while in the center is the bronchial artery that is enlarged relative to the pulmonary artery it accompanies and is also filled with an organized thrombus. The great dilatation and

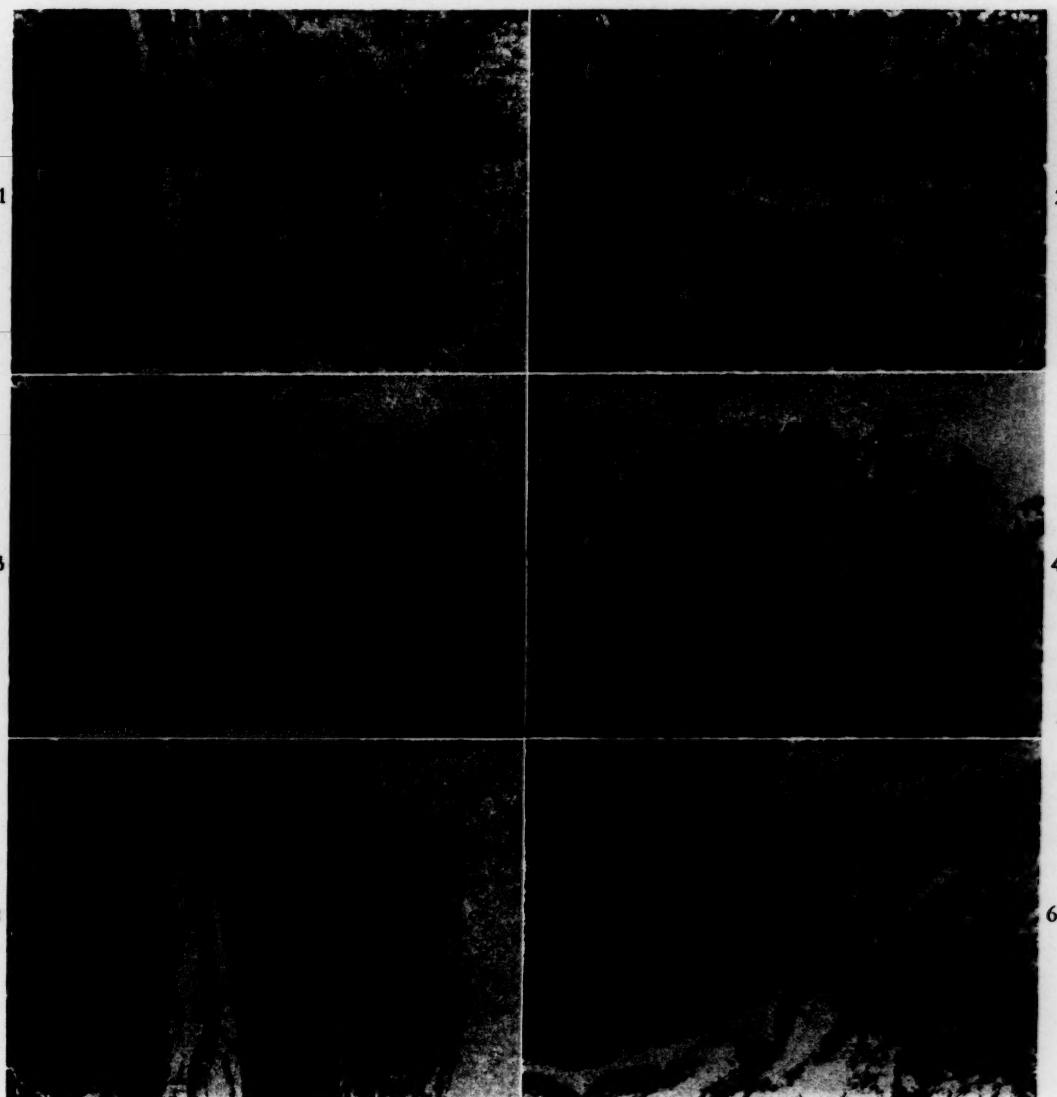


FIG. 1. A markedly thickened arteriole of the capsule of the adrenal that was typical of the arterioles in many organs.

FIG. 2. Arteriosclerosis and arteriolosclerosis without extensive secondary changes in the kidney.

FIG. 3. The edge of an old cystic focus of encephalomalacia. The well developed glial wall and the total removal of fat and necrotic tissue indicate this lesion was six months or more in age.

FIG. 4. A pulmonary artery in the periphery of the right lung. Within the lumen is a thrombus with well developed fibrous organization two months or more in age.

FIG. 5. The wall of the right main pulmonary artery with its contained thrombus which from its appearance might be four to eight weeks old.

FIG. 6. A dilated bronchial artery filled with an organized thrombus in the right lung; stain for elastic tissue. The edge of the accompanying pulmonary artery is apparent in the upper left corner and also contains an organized thrombus.

thrombosis of the bronchial arteries in this section as well as in others of the right lung are evidence of a disturbed pulmonary circulation of considerable duration.

Figure 7 shows a thebesian vein in the apex of the right ventricle under the mural thrombus described grossly. The vein is completely occluded by a thrombus which has undergone

extensive organization and must have been present for some weeks.

The microscopic appearance of the thrombi in the pulmonary vessels do not enable one to state whether they originated as emboli or autochthonous thrombi. After they have reached the stages of organization and dissolution which these thrombi had, it is no longer possible to

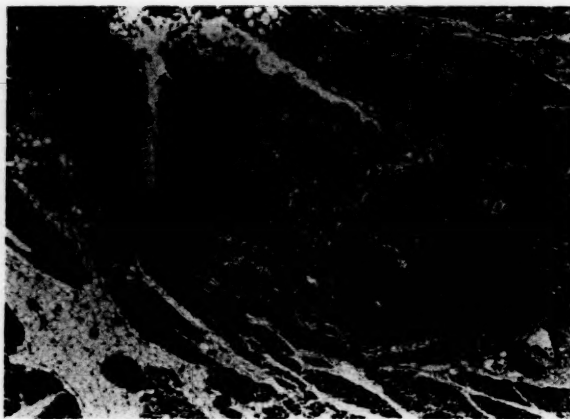


FIG. 7. An organized thrombus in a thebesian vein beneath the mural thrombus in the apex of the right ventricle.

make the helpful gross observation of valvular markings on the removed thrombus; and the most that can be said with absolute certainty is that at least part of the structure filling the vessel originated at that site. There were a few foci of organized pneumonia involving three or four alveoli in these sections; therefore it might be considered that at some time in the past this patient had pneumonia with an arteritis which established a thrombus. It seems unlikely, however, that pneumonia of enough severity to establish that much change in the vessels would have passed unnoticed in the clinical history. As there are no significant changes in the walls of the pulmonary arteries, we must assume that the smaller thrombi with the more advanced organization resulted from embolization. Subsequently there was sufficient interference with the pulmonary circulation to result in dilatation of the left pulmonary artery, dilatation and later thrombosis of the bronchial arteries in the right lung and propagation of the thrombus back into the main right pulmonary artery. There were no clinical signs or symptoms specifically indicating when the emboli came into the lungs, presumably because there was no previous congestion and consequently no infarction occurred. The stage of dissolution present in the thrombus in the main right pulmonary artery is consistent with a duration of four to eight weeks and, therefore, compatible with clinical evidence that the heart underwent an increased strain on the

right ventricle sometime in the month after the first electrocardiogram.

The mural thrombus in the right ventricle is compatible with strain on that side of the heart inasmuch as, in general, the formation of thrombi in a ventricular cavity proceeds as a result of the eddy currents that arise with failure. The thrombi in the thebesian veins are interesting; this is the third patient I have seen with thrombi in the thebesian veins associated with attacks of syncope. When the thebesian veins are blocked, the circulation of the inner quarter of the myocardium is compromised; and since that is the location of the Purkinje system, it seems possible that syncope might be related to some type of heart block.

In summary, the anatomic evidence indicates this patient had hypertension and arteriosclerosis for a period of years; that this arteriosclerosis became manifest many months before her death by the formation of foci of encephalomalacia; that sometime from four to eight weeks before her death there were emboli formed from thrombi, probably in the legs; and these emboli were carried to the lungs. Pulmonary infarcts were not produced, but on the right side a propagating thrombus developed which three to five weeks before her death totally occluded the right pulmonary artery and led to dilatation of the left artery and changes in the bronchial circulation. Finally a few hours or days before death there was a major alteration in the pulmonary circulation so that the embolic occlusions of the branches in the left lower lobe became operative and she developed two very recent pulmonary infarcts and died.

Anatomic Diagnoses: Arteriosclerosis of the pancreas, spleen, kidneys and adrenal glands; hypertrophy and dilatation of the heart; partially organized occluding thrombus in the right pulmonary artery and its primary branches; mural thrombus in the apex of the right ventricle.

Acknowledgment: Illustrations were made by the Department of Illustration, Washington University School of Medicine.

Special Feature

American Federation for Clinical Research

ABSTRACTS OF PAPERS PRESENTED AT THE EIGHTH ANNUAL MEETING OF THE MIDWESTERN SECTION
IN CHICAGO, NOVEMBER 2, 1950

CARDIOTOXIC ACTION OF INTRAVENOUS PROCAINE. *Fred S. Carter, M.D. and Jack L. Eisaman, M.D., La Porte, Ind.*

The effect of intravenous procaine on the electrocardiogram of unanesthetized humans was investigated. Electrocardiograms were made before and after procaine administration in forty-two patients. In most patients procaine was given daily. Either 4 mg. per kg. in twenty minutes or 1 gm. in one hour was administered intravenously. Thirteen patients received the former dose, twenty-nine the latter. There were four instances of P wave alteration, five of P-R interval prolongation, seventeen of QRS voltage decrease, two of QRS voltage increase, sixteen of T wave voltage decrease and eight of T wave voltage increase. Two cases presented marked prolongation of P-R interval, necessitating cessation of therapy.

It is concluded that procaine acts as a direct myocardial depressant. It should be used cautiously in heart disease.

LONG-TERM FOLLOW-UP OF EPIDEMIC INFECTIOUS HEPATITIS. *A. W. Barile, M.D., J. T. Taguchi, M.D., S. N. Maimon, M.D., E. A. Gall, M.D. (all by invitation) (introduced by Malcolm Block, M.D.), Dayton, Ohio.*

A long-term follow-up with liver biopsies in a group of twenty-five male patients with a definite past history of viral hepatitis, only seven of whom were admitted for suspected liver disease, is reported. Active viral hepatitis was demonstrated in four cases twelve to forty-eight months after their initial attack. In two cases the clinical course suggested re-infection and one case represented the protracted course chronic relapsing viral hepatitis may assume. In the last case the changes were thought to be due to infectious mononucleosis.

In no instance was there any histologic evidence of fibrosis although ten patients in the series had had recurrent jaundice. It was found that the greater the interval of time from the initial attack of hepatitis, the fewer were the non-specific changes found on biopsy, suggesting

that more complete restitution with the passage of time might be expected.

At the present time there is general agreement that the vast majority of patients who suffer from an attack of viral hepatitis recover completely without residual pathologic changes. A very small number develop serious irreversible changes in the liver within a few weeks to years after the initial infection. Post-necrotic cirrhosis is the most common and generally accepted form of liver cirrhosis which follows viral hepatitis. Cholangiolitic cirrhosis as an entity and its relation to hepatitis is not yet clearly defined. The greatest problem of whether classical Laennec's cirrhosis follows viral hepatitis to any significant degree, if at all, needs further studies in which histologic data are available.

OBSERVATIONS ON THE METABOLISM OF AN ORAL MERCURIAL DIURETIC. *E. R. Huffman, M.D., Springfield, Mo.*

The metabolism of mercury given orally for diuretic purposes is presumed to be similar to that given parenterally. The mercury complex given orally is the same complex given parenterally and basically intravenous and intramuscular mercurials are alike. It is the purpose of this paper to present certain differences between the metabolism of mercury complexes given orally from those given parenterally.

A total of eighteen decompensated cardiac patients with peripheral edema were given oral mercurhydrin in varying dosages of 156, 390 and 780 mg. of mercury. On the above dosages the average total percentage excretion of mercury was 78.4, 53.0 and 50.1, respectively, while the corresponding percentages in the urine were 1.6, 1.1 and 0.6. These results are compared with recovery values in eight patients who were given 312 mg. of mercury intramuscularly in ten study periods. The total average percentage excretion of mercury was 77.4. The average percentage of mercury appearing in the urine was 72.2.

A study of fecal weights during the period of administration of oral mercurhydrin revealed an increase over the control fecal weights in nine out of twelve instances.

EFFECTS OF CORTISONE AND ACTH IN ESSENTIAL HYPERTENSION: ESTABLISHMENT OF RENAL GLYCOSURIA. *Harriet Dustan, M.D. (by invitation), A. C. Corcoran, M.D., R. D. Taylor, M.D. and Irvine H. Page, M.D., Cleveland, Ohio.*

Of four patients with severe essential hypertension treated, two with cortisone and two with ACTH in doses of 100 mg. daily, three showed no change in arterial pressure during treatment. Two showed significant decreases in the immediate post-treatment period. During the first course of cortisone one showed a decrease of arterial pressure but two repetitions of the course of treatment failed to alter arterial pressure, from which it seems that the decrease first observed was incidental.

Sodium retention occurred in three patients during treatment (two with cortisone and one with ACTH) and evidences of negative nitrogen balance in two patients (one with cortisone and one with ACTH). Of the specific renal functions, (renal blood flow, glomerular filtration and Tm_{PAH}) renal blood flow was increased in two patients (one with cortisone and one with ACTH).

All four patients showed decreased serum cholesterol concentrations during treatment and a "rebound" to greater than control levels in the post-treatment period.

Three of the four patients showed a decrease of maximum renal tubular reabsorptive capacity for glucose (Tm_G) during treatment. This persisted into the post-treatment period and was associated with glycosuria. Depression of this renal function seems to be an early and lasting result of hypercorticism.

EFFECTS OF SPLANCHNICECTOMY ON THE BLOOD PRESSURE IN HYPERTENSION: A CONTROLLED STUDY. *S. W. Hoobler, M.D., J. T. Manning, M.D. (by invitation), W. G. Pain, M.D., S. G. McClellan, M.D., Henry Renfert, Jr., M.D. and E. A. Kahn, M.D., Ann Arbor, Mich.*

The blood pressure of 294 hypertensive patients was obtained ten to sixteen months after supradiaphragmatic splanchnicectomy and compared to the blood pressure of fifty-nine "control" hypertensives re-examined after one year in a similar manner. Of the patients who were operated upon 29 per cent experienced reductions of blood pressure exceeding that observed

in the control group and 7 per cent fell into the normotensive range. It was impossible to select patients for splanchnicectomy on the basis of any simple preoperative test employed except that in the presence of cardiac enlargement, cerebrovascular complications or papilledema the improvement rate fell from 10 to 20 per cent. Significant reductions in blood pressure in the early postoperative period were frequent: 53 per cent at three months and 44 per cent at six months. The 29 per cent reduction at one year appeared to be maintained through the second postoperative year. Extension of the operation upward to include ganglia D_6 - D_{12} bilaterally resulted in 50 per cent of cases with "significant" blood pressure reductions at one year postoperatively.

These data indicate that splanchnicectomy is a useful palliative procedure in hypertension and that upward extension of the conventional ganglionectomy may improve the results without requiring a two-stage operation or producing postoperative orthostasis.

STUDIES OF RENAL FUNCTION IN WEIL'S DISEASE.

Robert J. Griffin, M.D. (by invitation), Lloyd T. Iseri, M.D., Albert J. Boyle, M.D. (by invitation) and Gordon B. Myers, M.D., Detroit, Mich.

In five cases of Weil's disease C_{Man} , C_{PAH} , C_{Na} , and Tm_{PAH} were determined as soon as hydration was established during the first and second week of illness and were repeated during convalescence.

The findings were comparable in the five cases. Initial studies showed a marked depression in C_{Man} and moderate depression in C_{PAH} and Tm . The initial filtration fraction varied between 4 and 16.5 per cent. Two alternative explanations were considered for the strikingly low filtration fraction and C_{Man}/Tm_{PAH} ratio: (1) glomerular lesion and (2) tubular reabsorption of mannitol. Histologic sections of other patients who died during the acute stage of Weil's disease showed diffuse thickening and increased cellularity of the glomeruli. On assumption that comparable glomerular lesions were present in these cases and that C_{Man} is valid, calculated C_{Na} indicated an extremely low sodium reabsorption by the tubules, thus pointing to an associated tubular dysfunction.

Improvement in these specific function tests was rapid during convalescence as shown by rise in C_{Man} , C_{PAH} and Tm_{PAH} . Filtration fraction, however, remained low.

It is concluded that renal insufficiency in

Weil's disease is due primarily to glomerular disease.

CARDIOVASCULAR PERFORMANCE CAPACITY AND RENAL PLASMA FLOW IN PATIENTS WITH ASYMPTOMATIC AORTIC INSUFFICIENCY. *Thomas B. Gibbons, M.D. (by invitation), Austin Henschel, M.D. (by invitation) and Carleton B. Chapman, M.D., Minneapolis, Minn.*

To determine if patients with minimal but definite organic heart disease display aberrations of cardiovascular functions known to be markedly altered in patients in congestive heart failure, the maximal oxygen intake and the renal plasma flow were measured in eleven normal young men and in nine male patients of similar age, physique and exercise habits with asymptomatic aortic insufficiency due to rheumatic fever. In the absence of pulmonary disease the maximal oxygen intake is an objective measure of cardiovascular performance capacity and was measured by analysis of expired air collected for one minute beginning 105 seconds after the start of a three-minute run on a motor-driven treadmill. Various grades were employed. The mean maximal oxygen intake for the cardiac patients was 37.1 ± 3.32 cc./kg./minute, a value statistically significantly less than the normal subject mean of 45.3 ± 5.1 cc. Employing a constant injection of paraaminohippurate, renal plasma flow was determined at rest and during two sixteen-minute periods of walking at 3 miles per hour on a 10 per cent grade. Corrected to 1.73 sq. M. body surface, the mean resting renal plasma flow was 487 ± 79.9 cc. and 576 ± 60.5 cc. for the cardiac and normal groups, respectively; the difference is statistically highly significant. During exercise the percentage reduction in renal plasma flow was similar for the two groups although the absolute flow during exercise was much lower in the cardiac patients. Other functions tested included: respiratory efficiency, work performance efficiency and resting oxygen consumption all of which were similar for the two groups.

A STUDY BY MEANS OF INTRACARDIAC CATHETERIZATION OF THE EFFECT OF KHELLIN ON CARDIAC OUTPUT AND THE PULMONARY CIRCULATION IN MAN. *Helen Cash, B.S. (by invitation) and Henry A. Zimmerman, M.D., Cleveland, Ohio.*

Clinical and animal observations have indicated that khellin® is a potent coronary vasodilator, increases cardiac output and relaxes

bronchial musculature. This drug is advocated for treatment of angina pectoris, bronchial asthma, emphysema and cor pulmonale.

An attempt was made to evaluate the effects of khellin® on the cardiac output and pulmonary circulation in man by means of intracardiac catheterization. The study included five patients with pulmonary hypertension secondary to mitral stenosis or chronic lung disease. It has been shown previously that such patients respond with an increased cardiac output and diminished pressures in the pulmonary artery after the administration of aminophyllin.

The five patients included had an elevated pulmonary artery pressure due to mitral stenosis, chronic pulmonary emphysema, bronchial asthma or chronic bronchiectasis. Basal studies were made and included electrocardiograms, pulmonary and femoral artery pressures and cardiac output. Two hundred mg. of khellin® were given intramuscularly and the above studies repeated at fifteen-minute intervals for a period of seventy-five to ninety minutes after the injection of the drug. It was found that no significant changes occurred in the cardiac output or pulmonary artery pressure in the five patients.

One of these patients with a moderately severe attack of bronchial asthma obtained no symptomatic relief from 200 mg. of khellin® given intramuscularly. He was placed on a 320 mg. daily oral dose of khellin® for a period of six days at which time he was restudied and no significant changes in the cardiovascular dynamics were observed.

EFFECT OF PRISCOLINE (2-BENZYL-4, 5-IMIDAZOLINE HYDROCHLORIDE) AND ISUPREL (ISOPROPYLEPINEPHRINE) ON CIRCULATION AND METABOLISM IN NORMAL MAN. *Arnold Iglauer, M.D. (by invitation), Joseph Kaufman, M.D. (by invitation), and Gisela K. Herwitz, B.S. (by invitation); (introduced by) Robert S. Green, M.D., Cincinnati, Ohio.*

No consistent change in cardiac output as measured by the high-frequency ballistocardiograph was found following oral, intramuscular or intravenous administration of priscoline® to thirty-two normal subjects. Oxygen consumption, blood pressure and heart rate showed little change. The skin temperature gradient was never abolished completely by priscoline® even when given in high dosage.

Isuprel® was given sublingually, by aerosol and by subcutaneous injection to thirty-six

normal subjects. Definite increase in cardiac output usually occurred after subcutaneous administration. Changes in the ballistocardiogram were interpreted as indicating increased flow with decreased peripheral resistance. Less marked increase in cardiac minute volume was produced by sublingual administration, and cardiac minute volume was not changed by aerosol inhalation. Isuprel® did not affect oxygen consumption.

The findings indicate that cardiac load is not increased by priscoline;® moderate increase in cardiac work may follow administration of isuprel® as recommended for clinical use.

SIMULTANEOUS DETERMINATION OF TOTAL BODY WATER BY ANTIPYRINE AND DEUTERIUM OXIDE IN PATIENTS WITH EDEMA. *W. W. Hurst, M.D. (by invitation); (introduced by) F. R. Schemm, M.D., Great Falls, Mont.*

Simultaneous determinations of total body water using deuterium oxide and antipyrine were made in twenty-eight instances on sixteen subjects, one with chronic nephritis and hypertension, eleven with arteriosclerotic and three with rheumatic heart disease. All had gross edema at the initial study except for one normal.

In ten patients the studies were made at maximum edema level and again after its removal. The average weight loss was 13.7 kg. (range 3.4 to 39.7 kg.). The average deuterium space reduction was 10.4 L. (range .9 to 30.2 L.); the antipyrine space loss 9.8 L. (range 1.7 to 27.4 L.). The average initial deuterium space was 62.4 per cent body weight and 60.1 per cent when edema free. The initial antipyrine space was 55.7 per cent body weight and 53 per cent when edema free.

In five other patients initial studies only were made. The average weights were 74.3 kg. (range 59.3 to 97.8 kg.); the average deuterium space 44.7 L. (range 39.7 to 60.2 L.); the average antipyrine space 37.9 L. (range 35.1 to 45 L.).

For the entire twenty-eight determinations the average deuterium space was 61.5 per cent body weight, and for antipyrine 54.1 per cent. The deuterium-antipyrine ratio averaged 1.14 (range .995 to 1.34). In only one instance was the ratio less than one.

Simultaneous serial comparisons of antipyrine concentrations in blood and other body fluids were made in thirteen patients at intervals up to eleven hours. Tissue fluids were followed

in seven; equilibrium was reached in one (six hours). Ascitic fluid levels were followed in five and pleural fluid in two; in none was equilibrium reached.

Similar studies with deuterium were done in ten patients. Tissue fluid was followed in six; equilibrium was reached in three (six, seven and four hours). Ascitic fluid was followed in three and pleural fluid in one; equilibrium was reached in all (seven, seven and one-half, four and four hours).

NON-SPECIFIC PERICARDITIS, EARLY DIFFERENTIATION FROM ACUTE MYOCARDIAL INFARCTION AND DANGER OF ANTI-COAGULANT THERAPY. *Malcolm C. McCord, M.D. (by invitation), James T. Taguchi, M.D. (by invitation) and Malcolm Block, M.D., Dayton, Ohio.*

The beneficial results of anti-coagulant therapy in acute myocardial infarction increase with the promptness of therapy following the onset of the infarction. However, anti-coagulant therapy may have a deleterious effect on the course of non-specific pericarditis. Therefore, early differentiation of the two diseases must be accomplished and may depend largely on clinical evidence.

An analysis of eight cases of non-specific pericarditis reveals widely variable clinical, laboratory, roentgenographic and electrocardiographic changes. In five cases substernal chest pain was a prominent feature and in three cases a picture closely resembling myocardial infarction was present. One of the cases presenting the clinical picture of an acute myocardial infarction was treated with heparin and dicumarol and died on the fifteenth hospital day. Autopsy revealed myocarditis and hemorrhagic pericarditis with a hemopericardium. The anti-coagulant therapy may have intensified the hemorrhagic process.

The salient features of value in distinguishing non-specific pericarditis from acute myocardial infarction in these cases were: (1) intensification of pain by respiration, (2) evidence of or a history of respiratory infection, (3) presence at the onset of the disease of fever, leucocytosis or a pericardial friction rub, (4) history of a relapsing or chronic course of the disease, (5) electrocardiographic changes and (6) occurrence in younger age groups.

MYOCARDITIS, A CLINICAL AND PATHOLOGIC STUDY OF THIRTY-SIX CASES OF MYOCARDITIS, WITH SPECIAL REFERENCE TO DIAGNOSTIC CRITERIA AND THERAPEUTIC MANAGEMENT. *Mischa J. Lustok, M.D., Jules Chase, M.D. (by*

AMERICAN JOURNAL OF MEDICINE

invitation) and Joseph M. Lubitz, M.D. (by invitation), Milwaukee, Wis.

In an effort to reconcile the discrepancy between the relatively high incidence of myocarditis found at autopsy (Saphir) and the infrequency with which the diagnosis is made at the bedside, a systematic study was made of a group of thirty-six patients. Ten patients died and there were eight autopsies all of which showed myocarditis.

Pathologically, the acute and subacute phases are characterized by cellular infiltration, edema and degeneration of the myocardium. In the chronic stage the scar tissue resulting from the inflammation is non-specific.

Clinically, in the mild cases, tachycardia, tic-tac rhythm, electrocardiographic or roentgenologic changes were the only abnormalities noted. In the moderately severe group, dyspnea, precordial discomfort, diastolic gallop rhythm and pulsus alternans were encountered. The electrocardiographic changes were extensive and persistent in this group. The congestive heart failure and shock in the severe group were indistinguishable from those encountered in other types of heart disease.

Treatment was essentially supportive. Digitalis was ineffective in the acute stage; sodium restriction and mercurial diuresis appeared to result in a satisfactory response. Although the clinical course was usually self-limited, severe cases showed a tendency to chronicity, and ten cases ended fatally in sudden exodus or uncontrolled congestive failure.

COMPARISON OF THE INDIFFERENT ELECTRODES V, CR, RS. E. Feldman, M.D. (by invitation), E. J. Chesrow, M.D. (by invitation), G. A. Pipilis, M.D. (by invitation) and P. H. Wosika, M.D., Chicago, Ill.

One hundred electrocardiograms taken at the Oak Forest Infirmary were surveyed. The following leads were available for study: I, II, III, unipolar leads aVL, aVR, aVF, V₁ through V₇, CR₁ through CR₇, and RS₁ through RS₇.

In leads from the right precordium both P and T waves were more positive in the CR and RS leads than in the V leads. The QRS complexes showed a similar tendency.

The variations between the V, CR and RS leads were attributed to the influence of the right arm potentials as seen in aVR. In almost all cases, aVR exhibited a predominantly negative deflection which would increase the positivity of the precordial leads when the right

arm was used as the indifferent electrode. The striking similarity between corresponding CR and RS leads led to the conclusion that the right scapula is not completely indifferent but exhibited a potential similar to that of the right arm.

SUBCUTANEOUS TUBES FROM FREE SKIN GRAFTS.

William J. Butler, M.D. (by invitation), St. Joseph, Mich.

Urethroplastic procedures for the correction of hypospadias may be divided into two groups; those that form the urethra from free skin grafts and those that utilize pedicle grafts. This experiment was undertaken in an effort to evaluate the healing processes that occur when free skin grafts are transplanted subcutaneously to form a tube. The rat was used as the experimental animal. A measured rectangular strip of full thickness skin was removed from the abdomen and drawn through a stab wound in the subcutaneous fat, the long axis parallel to the segmental blood supply. Five of the grafts were sutured into tube form and twelve were placed flat with hair surface up. All were sutured to the surface skin at both ends of the tunnel and could be calibrated as long as the ostia remained intact. Two of the flat grafts formed skin-lined tubes with patent ostia up to six weeks after implantation. The rest of the grafts failed to maintain ostia beyond two weeks, and were finally represented by either cysts or a tract of scar and epithelial pearls. The two tubes that survived were lined by atrophic skin on a thin layer of collagen fibers.

Similar complications probably occur when doing this type of grafting in man and an indwelling stent for prolonged periods seems most advisable.

ETIOLOGY AND INJECTION TREATMENT OF KELOIDS AND SKIN PAPILLOMAS. Wallace Marshall, M.D., Two Rivers, Wis.

Recent histologic studies, along with current clinical observations, indicate that keloids and papillomas are herniations of the integument. The size of the herniation determines just what the tumor will be, either a keloid (wide base) or a papilloma (narrow base).

Recent research has shown that these skin masses can be at least partially shrunk by a substance which is derived from liver extract. This material contains a skin factor (S) which exerts a vasoconstricting action on normal skin and also upon keloids and papillomas which is evidence clinically by actual shrinking of these

masses. One case of pronounced keloidosis showed changes in the tumors when under therapy; these became narrowed at their bases, and resembled papillomas.

CLINICAL ASPECTS OF PORPHYRIA. *R. Craig Barlow, M.D., Ann Arbor, Mich.*

Porphyria has until recently remained a relatively obscure disease. The disease exists as two basic types, congenital porphyria and acute intermittent porphyria. Uroporphyrins, coproporphyrins and porphobilinogens are excreted in the urines, and may be detected by the Watson-Schwartz reaction.

Although the signs and symptoms of congenital porphyria are rather definite and constant, consisting of dermatitis, pigmentation of the teeth and interdental papillae and bones and excretion of dark red urine, the acute intermittent type is more difficult to recognize. The signs and symptoms of the latter disease are variable. It is emphasized that mental aberrations varying from mild anxieties to frank paranoid psychoses occur. There may be an ascending or Landry type of paralysis. Many of these patients complain of colicky pain. Red urine may not be present if only porphobilinogen is excreted.

Three patients with acute intermittent porphyria are discussed, all of whom exhibited mental and nervous symptomatology. One patient was given electroshock therapy before the diagnosis was established.

EXPERIMENTAL TREATMENT WITH TERRAMYCIN OF OBSTRUCTIVE APPENDICITIS IN RABBITS.

Charles H. Stevens, M.D. (by invitation), Eldon Caffery, M.D. (by invitation) and Merle M. Musselman, M.D., Eloise, Mich.

The value of chemotherapy in prolonging or saving life in closed loop intestinal obstruction has been adequately demonstrated in dogs. Farris demonstrated the efficiency of streptomycin in prolonging life after ligation of the appendix in rabbits. The present study was undertaken to estimate the efficiency of terramycin therapy in obstructive appendicitis and peritonitis in rabbits.

Appendices of rabbits were ligated and distended with lipiodol after the method of Farris. Terramycin hydrochloride was given to one-half the animals in a dosage of 150 mg. or 300 mg. per day in three divided doses for five days. Serial x-rays were taken. Cultures were carried out routinely, *E. coli* and proteus being the most frequently demonstrated organisms.

The results in this series suggest that terramycin is effective in prolonging life in rabbit in which a "closed loop" appendicitis has been created.

GASTRIC SECRETORY RESPONSE TO INSULIN HYPOGLYCEMIA AS INFLUENCED BY HIGH DOSES OF INSULIN PRODUCING EXTREME HYPOGLYCEMIA. *Paul R. Sharick, M.D. (by invitation), Eloise, Mich.*

Neches and co-workers stated that high doses of insulin and low levels of blood sugar caused a depression of gastric secretion in dogs. The purpose of this study was to evaluate the effect of large doses of insulin and low levels of blood sugar on the gastric secretory response in humans.

Nine psychotic patients receiving subcutaneous insulin in sufficient quantity to produce coma were studied. Gastric specimens were drawn at fifteen-minute intervals and blood specimens for sugar were drawn at thirty-minute intervals. Insulin dosage as high as 310 units of crystalline insulin and blood sugar levels as low as 12 mg. per cent were attained. Five patients showed a marked increase in gastric acid, three a moderate increase and one patient failed to show a response.

The depth of hypoglycemia obtained and the dosage of insulin used in this study did not depress the expected gastric secretory response to hypoglycemia.

AGNOGENIC MYELOID METAPLASIA OF THE SPLEEN. *John D. Battle, Jr., M.D., Cleveland, Ohio.*

The term "agnogenic," introduced by Jackson and Parker in 1940, denotes the unknown etiology of the condition and is used to distinguish it from myeloid metaplasia of the spleen secondary to polycythemia vera, metastatic tumors of the bone marrow, etc. Prior to 1940 such descriptive terms as chronic non-leukemic myelosis, myelophthisic splenomegaly, leucoerythroblastosis and myelosclerosis were used.

The clinical and laboratory features may simulate acquired hemolytic anemia, thrombopenic purpura, and most often, chronic granulocytic leukemia. Hepatomegaly, splenomegaly, anemia with leukopenia or leukocytosis are often present. The peripheral blood usually shows granulocytic immaturity and frequent normoblasts. Marrow aspiration is rarely diagnostic but marrow biopsy usually reveals myelosclerosis or myelofibrosis. The diagnosis is definitely established only by microscopic study

of the spleen which can be obtained by splenic puncture. The architecture of the spleen is maintained and foci of immature granulocytes, normoblasts and megakaryocytes are observed.

Several reports indicate that chronic benzene poisoning may cause this condition. No exposure to benzene was present in the patients observed in this series. It is generally agreed that recognition of this condition is important because splenectomy and x-ray therapy are usually harmful.

THE HARGRAVES "L. E." CELL: OBSERVATION OF ITS FORMATION. *John B. Moyer, M.D. and George S. Fisher, M.D., Duluth, Minn.*

L. E. cells may be found in marrow buffy coat concentrate preparations from cases of disseminated lupus erythematosus as well as in the blood buffy coat. They can be induced in human or animal marrow preparations, and under certain circumstances in peripheral blood, by mixture with the "L. E. factor." Three elements are necessary for L. E. cell formation: (1) active phagocytes to ingest (2) nucleoprotein in the presence of (3) the L. E. factor.

The L. E. cell inclusion appears to be derived from nucleoprotein. It appears that any effective source of nucleoprotein must contain lymphocytic nuclei. A relatively pure suspension of lymphocytes was obtained from a case of chronic lymphocytic leukemia. After alteration by freezing to remove the cytoplasm, the nuclei were ingested in abundance by neutrophils in the presence of the L. E. factor. Similar alteration by freezing of relatively pure suspensions of neutrophils failed to provide a suitable source of nucleoprotein. Supravital observations were made of a mixture containing fresh neutrophils, altered, bare lymphocytic nuclei and the L. E. factor. Active phagocytosis of the bare nuclei by neutrophils and formation of typical L. E. cells was witnessed.

This evidence lends support to the proposition that the L. E. cell is the result of ingestion of a lymphocyte nucleus by a phagocyte.

LIVER FUNCTION DURING CORTISONE THERAPY. *S. C. Percefull, M.D. and J. H. Holmes, M.D., Denver, Colo.*

Studies of liver function were carried out in fifteen patients before, during and after cortisone therapy. The following determinations were included in these studies: thymol turbidity, serum bilirubin, bromsulfalein, van den Bergh,

icteric index, prothrombin time, total cholesterol, cholesterol-ester ratio and serum esterase.

Our results indicate that cortisone therapy, even for periods up to three months or in amounts up to 10 gm., produces no startling abnormality in any of these liver function tests. This was true even in two patients with liver disease. In several instances there was a slight elevation in the values for thymol turbidity during cortisone therapy which returned to normal after the drug was stopped. In two instances in which there was an elevation of thymol turbidity prior to therapy the values decreased in association with cortisone administration. A significant elevation in the serum cholesterol was found in three instances and minor elevations in five. The serum esterase values decreased slightly in the majority of cases.

EFFECT OF CORTISONE ACETATE ON ACUTE EXUDATIVE STREPTOCOCCAL TONSILLITIS AND PHARYNGITIS: CLINICAL AND IMMUNOLOGIC ASPECTS. *Edward O. Hahn, Capt. M.C., AUS (by invitation), Charles H. Rammelkamp, Jr., M.D., Harold B. Houser, Capt. M.C., AUS (by invitation), Lewis W. Wannamaker, Capt. M.C., AUS and Floyd W. Denny, Capt. M.C., AUS, Cheyenne, Wyo.*

The pituitary and adrenal hormones play an important role in the reactions of the body to stress. One of the common stress reactions in man is infection. Since there is little information concerning the effect of these hormones in infections, the adrenal hormone, cortisone, was administered to eighty-seven patients with streptococcal exudative tonsillitis; another eighty-seven served as controls. A total of 500 or 600 mg. of cortisone was administered over five days. Observations included the effect on the acute illness, the suppurative and late non-suppurative complications and antibody formation.

Therapy resulted in no alteration of the symptoms or physical signs. However, the treated group exhibited prolonged fever. Three suppurative complications developed in the controls. During cortisone treatment one patient developed gangrenous appendicitis with signs of peritonitis. Rheumatic fever developed in two treated and five control patients. An additional six treated and two control patients showed prolonged P-R intervals three weeks after the illness. In those who received cortisone the anti-streptolysin titers were slightly lower than in the

controls at six days but higher at two, three and four weeks.

EFFECTS OF CORTISONE IN GLOMERULONEPHRITIS AND THE NEPHROPATHY OF DISSEMINATED LUPUS ERYTHEMATOSUS. *B. I. Heller, M.D., W. E. Jacobson, M.D. and J. F. Hammarsten, M.D. (by invitation), Minneapolis, Minn.*

Cortisone was administered to four patients in various phases of glomerulonephritis and to two patients with disseminated lupus erythematosus with renal involvement. The patients were placed on a constant diet, and control observations of the blood pressure, renal plasma flow, glomerular filtration rate and electrolyte balance were made. Moderate hypertension developed in one patient with the nephrotic phase of chronic glomerulonephritis, and severe hypertension ensued in both patients with lupus erythematosus. Transient alterations in renal function, manifested by increases in renal plasma flow, or glomerular filtration rates, or both, were observed. However, the basic pathologic process in the glomerular capillaries was unaltered as indicated by persistence of hematuria and albuminuria in all cases. In some instances albuminuria actually increased. The effects of cortisone upon electrolyte balance were similar to those previously reported in the literature except for observations in one patient with disseminated lupus erythematosus. The administration of cortisone in this patient was associated with a significant rise in serum potassium and fall in serum sodium concentration. This phenomenon was again observed when cortisone therapy was re-instituted.

It is concluded that cortisone does not favorably alter the course of glomerulonephritis and the nephropathy of disseminated lupus erythematosus.

EFFECT OF ADRENAL CORTICAL EXTRACT, ACTH, CORTISONE AND H. P. C. (3-HYDROXY-2 PHENYLCHINONIC ACID) ON JOINT PERMEABILITY. *J. Hidalgo, B.S., C. D. McClure, B.S., J. B. Henderson, B.S., R. W. Whitehead, M.D. (all by invitation); (introduced by) Charley J. Smyth, M.D., Denver, Colo.*

In an attempt to evaluate the action on membrane permeability of an adrenal cortical extract (ACE) prepared in this laboratory, we tried to measure the rate of excretion of phenol-sulfonphthalein (P. S. P.) injected into the synovial capsule of the rabbit. The method of Seifter was used except that the knee joint was entered.

Eleven rabbits were standardized by injecting P. S. P. and urine samples were collected at ten-minute intervals for a period of 135 minutes. The same rabbits after three weeks rest were injected with the drug under study before the P. S. P. was given. Nembutal was used as an anesthetic and supplemented by ether when necessary.

The ACE prepared by us, as well as a similar extract supplied by Wilson Laboratories, proved to have no effect on the time of appearance of the dye in the urine or on the rate of its excretion. Cortisone (Merck) and hydroxy-phenylcinchoninic acid (H. P. C.) were also found to be devoid of effect on membrane permeability to the dye. Within the limits of experimental error both the control curves and those obtained following the drugs could be superimposed.

METABOLIC EFFECTS OF ACTH UPON PRE-EXISTING DIABETES MELLITUS. *Stefan S. Fajans, M.D. and Jerome W. Conn, M.D. (by invitation); (introduced by) William D. Robinson, M.D., Ann Arbor, Mich.*

Administration of ACTH produces a diabetic state and insulin resistance in some normal individuals. Both ACTH and Cortisone have been observed to intensify hyperglycemia and glycosuria when given to diabetics. Ketonemia and ketonuria have been found to increase sharply when cortisone is administered to patients having both diabetes mellitus and Addison's disease.

Careful study of the metabolic effects of ACTH upon pre-existing diabetes mellitus seemed important but justification was lacking. To satisfy the latter requirement extensive metabolic balance studies were performed upon a severely diabetic patient who received a large amount of ACTH over a twenty-two-day period for the purpose of influencing a recently developed leukemia.

The more significant observations were as follows: (1) Great intensification of the diabetic state; on the last ACTH day glycosuria exceeded carbohydrate intake by 100 gm.; (2) tremendous negative nitrogen balance; on the last ACTH day nitrogen excretion exceeded nitrogen intake by 23 gm.; (3) insulin resistance; (4) surprising absence of significant ketonemia and ketonuria; (5) increased activity of the leukemia; (6) hypertrophy of the adrenal cortices at autopsy. ACTH appears either to decrease ketogenesis or to increase ketolysis.

**X-RAY THERAPY TO THE PITUITARY IN THE
TREATMENT OF MALIGNANT EXOPHTHALMOS.**

William H. Beierwaltes, M.D., Ann Arbor, Mich.

Ten patients with classical malignant exophthalmos and one with progressive exophthalmos were followed at monthly intervals by measurement with the Hertel exophthalmometer, for periods of seven to forty-eight months, averaging twenty-four months. Photographs of the eyes were made before and after treatment in six patients, and extra-ocular muscle biopsies compatible with the diagnosis of malignant exophthalmos were obtained in three patients. All patients were treated first with desiccated thyroid for a control period averaging seventeen months with no significant decrease in exophthalmos. X-ray therapy was then given to the

pituitary through bitemporal ports in eight patients and an additional frontal port in two patients. Total radiation varied from 800 to 2,000 r. Exophthalmometer measurements were continued for an average of twelve months after radiation.

In the post-irradiation period eight patients enjoyed a significant (2 mm. or more) decrease in exophthalmos averaging 4.2 mm. O. D. and 3.1 mm. O. S. Three patients obtained no significant decrease in eye protrusion, but showed increase in exophthalmos of only .33 mm. O. D. and .66 mm. O. S. No correlation was found between the exophthalmometer measurements and simultaneous body weight, B. M. R., basal pulse and plasma cholesterol levels.

Case Reports

Lymphocytic Leukemoid Reaction Associated with Primary Carcinoma of the Breast*

CHARLES R. KLEEMAN, M.D.

Newington, Connecticut

THE interest in the case described herein centers about the association of a lymphocytic leukemoid reaction with carcinoma of the breast. This combination of lesions presented a baffling clinical picture not clarified until the postmortem examination disclosed diffuse metastatic involvement of marrow, lymph nodes, spleen and liver from the primary carcinoma in the breast.

The simulation of the leukemic state or the clinical syndrome of leukemia by an unrelated clinicopathologic condition is spoken of as a leukemoid state or reaction. It should be stressed that uncommon as the leukemoid reactions of the myeloid type are in carcinoma lymphocytic leukemoid reactions are a far greater rarity.

Krumbhaar³ and others² do not discuss malignant tumors in the production of lymphocytic leukemoid reactions while referring to measles, pertussis, acute infections with lymphocytosis and such chronic lesions as tuberculosis as producing the lymphocytic leukemoid state.

A study of the American literature and a partial survey of the foreign literature discloses only six specific references to lymphocytic leukemoid reactions associated with malignant or benign neoplasms.^{7-10,15,16} Winan's case¹⁰ is the only one referring to a benign tumor in the production of a lymphocytic leukemoid reaction. However, it is difficult to consider his case as definitely a lymphocytic leukemoid reaction since the resemblance to infectious mononucleosis leaves doubt as to the nature of the lymphocytosis.

Lisa, Solomon and Gordon⁷ reported a case of carcinoma of the lung with diffuse metastases to the bone marrow, spleen and liver that was clinically and hematologically indistinguishable from lymphatic leukemia. The white cell count was 28,450 with 60 per cent lymphocytes, chiefly prolymphocytes.

Reich's case⁸ of adenocarcinoma of the sigmoid showed extensive replacement of the bone marrow and generalized visceral metastases. No specific reference to splenic metastasis is made. Clinically, the white blood count ranged from 18,700 to 53,800, lymphocytes 77 to 95 per cent. An antemortem bone marrow biopsy was described as showing marked infiltration with lymphocytes, many of which were abnormal. Autopsy disclosed diffuse involvement of the marrow by metastatic carcinoma but no histologic evidence of leukemia in any organs.

Sala and Stein⁹ presented a case of ductal carcinoma of the breast which at autopsy showed most of the marrow replaced by tumor and diffuse involvement of the spleen and liver. The white blood cell count ranged from 29,600 to 33,400, 60 to 65 per cent lymphocytes, young and mature, and some abnormal granulocytes. This case showed active extramedullary hematopoiesis in the liver and spleen.

Muller and Werthemann¹⁵ report a case of carcinoma of the breast with extensive metastases to the bone marrow, spleen and lymph nodes which during life presented a white blood cell count of 33,000 with 63 per cent lymphocytes.

Recently there has appeared in the

* From the Mallory Institute of Pathology, Boston City Hospital, Boston, Mass.

hematologic literature a report of three cases by Bichel¹⁶ in which he discussed lymphatic leukemia and lymphocytic leukemoid reactions in cancer of the stomach. One was a definite lymphatic leukemia complicated by carcinoma of the stomach, both being proved at autopsy. The second case appeared to be a lymphocytic leukemoid reaction that developed two years prior to gastric symptoms due to carcinoma of the stomach. The patient's blood counts fell from 64,000 to 12,800 prior to death, and the lymphocyte count fell from 94 per cent to 2.3 per cent. At autopsy, metastases from the carcinoma of the stomach were present only in the regional nodes and left lobe of the liver. There were no leukemic infiltrates in any organs.

His third case, although he considered it to be a lymphocytic leukemoid reaction, is difficult to classify as such since there was no autopsy and prior to death the bone marrow contained "80 per cent atypical mononuclear cells" and the biopsied lymph node showed "typical leukemic changes."

CASE REPORT

A fifty-seven year old white married woman was admitted to the Boston City Hospital on December 30, 1948, with the chief complaint of vomiting of four months' duration. The patient was apparently well until four months prior to entry when she noted loss of appetite and experienced episodes of nausea and vomiting once or twice weekly. There were no changes in bowel habits. No color changes were noted in the skin or stool.

An abscess of the left breast had been operated upon fifteen years prior to admission; it healed and was followed by scarring and retraction of the left nipple.

System review revealed some bleeding of the gums and episodes of slight epistaxis during a period of several months prior to hospitalization. On entry her temperature was 99°F., pulse 120, respirations 22 and blood pressure 160/90. The patient was a well developed, well nourished, moderately obese, pale white woman in no distress but appearing tired. There was slight gingival pallor and hypertrophy. There was a small scar in the upper inner quadrant of the left breast fixed to skin and inverting the

nipple. No adenopathy was noted. Examination of the heart and lungs showed nothing remarkable. The abdomen was obese; the liver was palpated two fingerbreadths below the costal margin; no other masses were palpable. Rectal and pelvic examinations revealed no abnormalities.

TABLE I
PERIPHERAL BLOOD FINDINGS

Date of Findings:	1/4	1/6	1/7	1/10	1/18	1/24
Red blood cells (millions).....	3.6
Hemoglobin (gm. %).....	9.4
Hematocrit.....	31.3
Reticulocytes.....	4.7	4.8
Nucleated red blood cells per 100 white blood cells.....	8	8	12	12	6	32
White blood cells.....	Ranged between 17,200 and 27,000					
Polymorphonuclear neutrophils.....	17	26	26	30	30	23
Polymorphonuclear neutrophils (band).....	11	12	16	15	29	56
Polymorphonuclear eosinophiles.....	1
Lymphocytes, small.....	40	48	38	37	20	15
Lymphocytes, large.....	18	2	7	6	10	1
Monocytes.....	9	7	10	9	9	3
Metamyelocytes.....	1	3	2	1	1	2
Blast.....	1
Abnormal cells.....	2	2	1	1	1	...
Platelets—Normal but large.....

The urine was normal. See Tables I and II for blood and marrow findings. Three stools were guaiac-positive.

The patient on bed rest was asymptomatic and her appetite was good. Her temperature ran

TABLE II
STERNAL ASPIRATION SMEAR

	Per Cent*
Polymorphonuclear neutrophils.....	12
Polymorphonuclear eosinophiles.....	1
Polymorphonuclear basophiles.....	5
Myelocytes, neutrophilic.....	0
Myelocytes, eosinophilic.....	0
Myelocytes, basophilic.....	0
Myelocytes, early.....	0
Myeloblasts.....	0
Lymphocytes.....	53
Plasma cells.....	0
Monocytes.....	6
Megakaryocytes.....	0
Reticulum cells.....	0
Normoblasts.....	7
Erythroblasts.....	0
Primitive red cells.....	0
Tumor cells.....	14

* The percentages listed here are those derived from a total count of 800 cells.

from 99° to 100°F. Her complexion was sallow. The spleen was now noted to be rather easily felt. X-rays of the chest revealed no evidence of consolidation. Gastrointestinal series revealed a

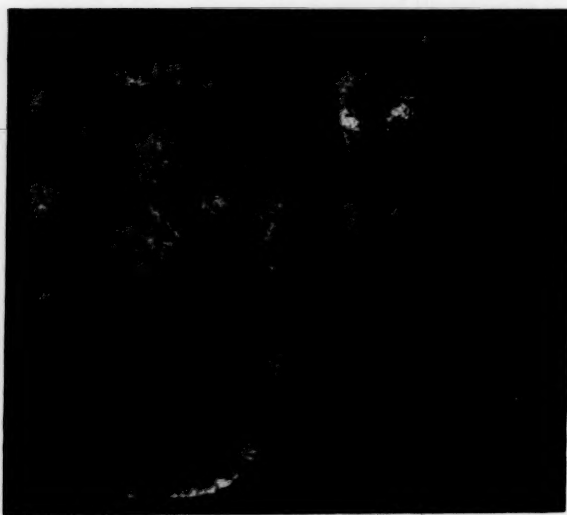


FIG. 1. The gross appearance of the spleen as seen at autopsy; note the diffuse waxy appearance and the telangiectatic spots.

hiatus hernia. Spinous process bone marrow aspiration revealed large blast cells. A metastatic series showed osteoporosis of the bones of the thorax with irregular areas of diminished radiance in the right hemipelvis and right femur.

Although the left breast mass was considered to be scar tissue by the surgical consultant, biopsy was advised. On the twenty-first hospital day the patient experienced a rise in temperature to 101°F., and the biopsy was cancelled. The patient was noted on the twenty-second day to be less responsive than previously. Chest examination revealed decreased resonance and rales at the left base. Minimal nuchal rigidity developed with a temperature of 103°F. A lumbar puncture revealed turbid yellow spinal fluid with 220 white blood cells per cu. mm., 100 per cent polymorphonuclear leukocytes and 383 red blood cells per cu. mm. The Pandy test was 4+. The fluid submitted for culture grew out a type 27 pneumococcus. Chemotherapy was of no avail and the patient lapsed into coma and expired on the twenty-fourth day.

In the autopsy report only the pertinent findings were included. Externally, the left breast contained a firm, irregular mass about 5 by 8 cm., poorly circumscribed and attached to the overlying skin, causing retraction of the upper portion of the nipple and areola.

The lungs weighed 460 gm. on the right and on the left 500 gm. The pleural surfaces of both right and left lower lobes were studded with small, 1 to 3 mm., white, slightly elevated, nodular plaques, giving the surfaces a cobble-

stone appearance. The mediastinal (hilar and peribronchial) lymph nodes showed white, irregular replacement of the anthracotic areas but were not enlarged.

The spleen weighed 295 gm. It was diffusely enlarged and very firm and almost hard in consistence. The surface was a creamy white color, very glistening and waxy with slight surface irregularity. On section the parenchyma throughout showed a remarkable waxy, yellowish white appearance. Speckled throughout this waxy parenchyma were small, irregular, telangiectatic-like vascular markings. (Fig. 1.)

The liver weighed 1,650 gm. The surface was yellow-brown in color. Scattered over the surface were numerous 0.5 to 1.0 cm. depressed, white, puckered areas. On section these areas were seen to extend from a few mm. to over 1 cm. into the parenchyma and to be fibrous-like in character. The remainder of the parenchyma had an orange-yellow color with indistinct lobular pattern and firm consistence.

Examination of the brain revealed there was diffuse injection of the meninges with localized accumulations of yellow, purulent material in the subarachnoid space. No intracerebral masses were seen.

The entire marrow of ribs, sternum, vertebrae and ilium was yellow-white, very firm and showed focal, irregular areas of fatty material.

On section the breast mass consisted of dense, firm, fibrous tissue, not circumscribed, retracted and covered with granular, chalky white material.

Histologically, examination of the breast showed there was extensive dense fibrosis surrounding the ducts. Arising from the ducts and infiltrating between the strands of fibrous tissue were cords of neoplastic cells, their nuclei being either hyperchromatic or vesicular with large nucleoli. The cytoplasm was rather abundant. In areas the nucleus was pushed to the side of the cell by single or multiple pinkish white vacuoles in the cytoplasm.

All lung sections showed extensive perivascular and lymphatic involvement with these neoplastic cells.

There was extensive generalized replacement of the liver parenchyma by cells as seen previously. The tumor involved all areas of the lobule. The islands of liver cells remaining showed fat vacuoles in the cytoplasm and bile stasis. The tumor cells in areas showed abundant lipid infiltration of the cytoplasm.

The entire spleen was replaced by the neoplastic process, completely destroying the architecture. A few hyalinized blood vessels were seen. The tumor pattern here was very similar to that seen in the liver; the cords and nests of tumor cells were surrounded by fine acidophilic connective tissue stroma.

Focal accumulations of neoplastic cells were seen in both adrenals.

Axillary, mediastinal and preaortic nodes showed partial replacement by tumor cells. In areas the latter filled the peripheral and medullary sinuses and surrounded active areas composed mainly of young lymphocytes, some arranged in follicle form. (Fig. 2.)

In the pituitary an isolated focus of tumor cells was seen in the posterior lobe.

All sections of the bone marrow showed almost complete replacement by the neoplastic cells, growing as seen in the liver and the spleen. Those few areas not involved showed normoblastic type of hyperplasia of the red blood cells.

The anatomic diagnoses were as follows: (1) there was adenocarcinoma of the left breast with diffuse metastases to the lungs, liver, bone marrow, adrenals, spleen, pituitary (posterior lobe), axillary, mediastinal and preaortic lymph nodes and serosa of the uterus. (2) Purulent meningitis (pneumococcic) existed.

COMMENTS

It should be emphasized again that the lymphocytic leukemoid blood picture which this case presented is of very rare occurrence in neoplastic disease. An explanation of the lymphocytic leukemoid reaction in this case and its clinical and hematologic diagnosis presents itself as the major problem in this study.

The peripheral blood counts as seen in Table I were counts done on an average of 400 cells each. The outstanding features of these counts were the presence of nucleated red blood cells which are of rare occurrence in lymphatic leukemia and often seen in myelophthisic anemias, the great number of lymphocytes, both young and old, and the presence in the peripheral blood of tumor cells similar to those seen in the antemortem bone marrow smears. As was noted in the section of bone marrow not involved with tumor there was a normoblastic type of hyperplasia without granulocytic hyperplasia.

APRIL, 1951



FIG. 2. High magnification of the periphery of a lymph follicle of a retroperitoneal node showing the tumor cells adjacent to the lymph follicle. Phloxine-methylene blue, $\times 1,000$.

The high lymphocyte counts seen early in the disease (Table I) showed a slow, but progressive fall, being replaced terminally by a relative and absolute polymorphonuclear leukocytosis, associated with the complicating pneumococcal meningitis. It is not likely, however, that the meningitis stimulated the leukemoid blood picture, as the former occurred as a terminal complicating event.

The progressive slow fall in lymphocytes was noted also by Bichel.¹⁶ He believed that although the reason for this fall was obscure, its occurrence has been seen in lymphocytic leukemoid reactions associated with carcinoma.

An unclassifiable, large abnormal cell with pale blue vacuolated spongy cytoplasm and a basophilic, honeycombed and at times vacuolated nucleus was seen occasionally in the peripheral blood. It was considered to be identical with the cells in the marrow aspiration described as tumor cells. (Fig. 3.) The resemblance of the tumor cells in the antemortem smear to the tumor cells seen on postmortem smear from the surface of the spleen is quite striking. (Figs. 3 and 4.) Because these abnormal tumor cells tended to occur in clumps or groups in the marrow aspiration, it made the counts difficult. It was for this reason that 800 cells on two separate slides were counted to arrive at the percentages listed in Table II. It is hard to reconcile the high

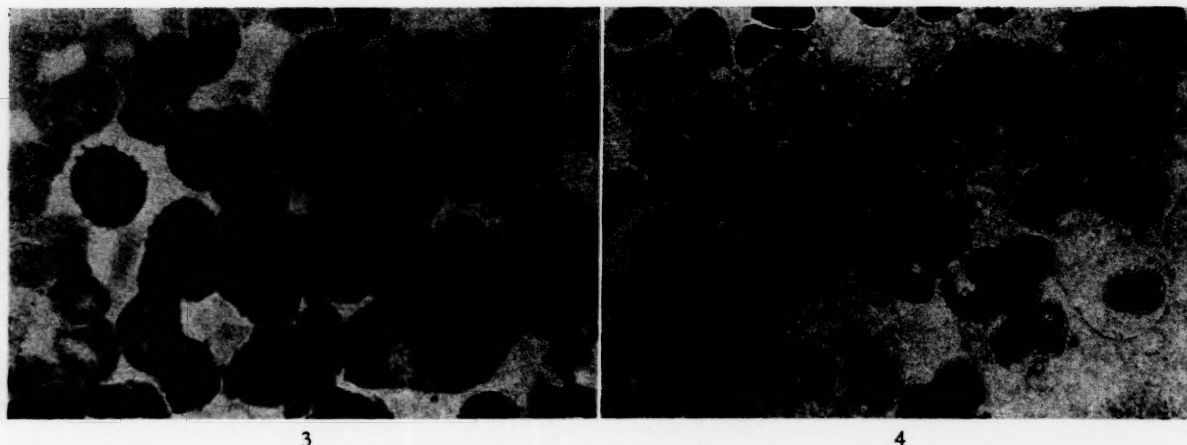


FIG. 3. A small group of tumor cells as seen on the antemortem bone marrow smear; note the fine vacuolation in both cytoplasm and nuclei. An adult lymphocyte is seen to the left of the tumor cells. Wright's stain, $\times 2,500$.

FIG. 4. A group of tumor cells as seen on postmortem smear of the cut surface of the spleen; note the similarity to the cells in Figure 3. Wright's stain, $\times 2,300$.

lymphocyte counts seen on marrow aspiration with the autopsy appearance of the marrow which showed very few lymphocytes. However, some of these cells seen on the antemortem smear may well have been tumor cells with an appearance quite similar to lymphocytes. The peroxidase stains on both peripheral blood and marrow smears were negative for granules in the lymphocytes and tumor cells.

The mechanism by which carcinoma is able to produce either a lymphocytic or myeloid leukemoid reaction is quite obscure. That the bone marrow probably need not be involved by metastatic tumor has been shown by many studies.^{1,3-5,11,16}

The pathogenesis of the lymphocytic leukemoid reaction in this case is entirely obscure. However, certain observations stand out in the previously described cases of lymphocytic leukemoid reactions in carcinoma which may shed some light on the present case.

In four of the previously reported cases^{7-9,15} the bone marrow was diffusely involved with tumor and three of the cases showed extensive carcinomatous involvement of the spleen. The case reported herein had extensive metastatic involvement of both marrow and spleen.

It might be postulated that in extensive bone marrow destruction a relative lymphocytosis may occur as described by Morrison,⁶ but it should be accompanied, as he

noted, with leukopenia and granulocytopenia due to myeloid destruction of the myelophthisic type. In this case there was an absolute lymphocytosis. The additional generalized lymph node involvement by the metastatic tumor may have stimulated this latter reaction. In regard to the diffuse splenic involvement a questionable mechanism of "hypersplenism," as is often postulated in "Banti's Syndrome" or "primary splenic cytopenias," may possibly be acting to depress the bone marrow. This latter point is probably not of great importance as no leukemoid blood picture was seen in the eighteen cases of carcinoma of the breast with splenic metastases in the Mallory Institute of Pathology between 1896 and 1948, with the exception of the case reported herein.

The focal metastases to the adrenals in this case were not considered extensive enough to produce hormonal depression with its effects on circulating lymphocytes and lymphoid tissue.

In this case we have almost complete replacement of the bone marrow by tumor growth. The sites of usual extramedullary hematopoiesis, the liver and spleen, were also replaced to such an extent that they could not carry out their embryonic hematopoietic function. Finally, the stimulation of the lymph nodes by the presence of the tumor cells may have led to the lymphocytic domination of the peripheral blood.

However, under the stimulus of the added bacterial meningitis the patient was able to show some leukocytic response. This probably indicated the presence of marrow foci of myeloid activity since no foci of extramedullary hematopoiesis were seen. Many more cases of this type will have to be studied before the problem of lymphocytic leukemoid reactions is clarified.

Finally, it should be asked, "Could this case be differentiated antemortem from lymphatic leukemia?" The presence of the high nucleated red blood cell count and the presence of cells described as tumor cells, both in the peripheral blood and bone marrow, point very strongly toward a myelophthisic reaction and away from lymphatic leukemia. The nucleated red blood cell reaction in the peripheral blood as seen in this case was also present in the case of Lisa, Solomon and Gordon⁷ and is thought by Morrison⁶ to be an important diagnostic feature in neoplastic bone marrow involvement. Ward¹² in his early description of leukemoid reactions also stressed the importance of nucleated red blood cells in the peripheral blood in metastatic tumor to the bone marrow. As pointed out by Whithy and Britton¹⁴ these nucleated red blood cells are a manifestation of a shifting of erythropoiesis "to the left" and represent a dyshemopoiesis due to foreign tissue in the marrow rather than a simple compensatory hyperplasia due to tumor tissue replacement of the marrow. Finally, the progressive fall in the lymphocyte count in the peripheral blood, as noted by Bichel¹⁶ and as seen in this case, may have been of diagnostic significance when combined with the previously mentioned findings.

SUMMARY AND CONCLUSIONS

1. A case of carcinoma of the breast is reported showing a lymphocytic leukemoid blood picture, and the rarity of this reaction in carcinoma is stressed.

2. The presence of a leukemoid blood picture and nucleated red blood cells in the peripheral blood in carcinoma, or the presence of the nucleated red blood cells

alone, should stimulate search for metastatic foci in the bone marrow by x-ray and biopsy.

3. From the available data a definite mechanism for the lymphocytic leukemoid reaction cannot be given.

Acknowledgment: The author wishes to acknowledge thanks to Drs. F. Parker, Jr., G. K. Mallory and S. Robbins of the Mallory Institute for their helpful criticisms and revisions and to Miss Geneva A. Daland of the Thorndike Memorial Laboratory for her assistance in interpretation of the bone marrow smears. Photographs were made by Mr. Leo Goodman, Mallory Institute of Pathology.

REFERENCES

- HILL, J. M. and DUNCAN, C. N. Leukemoid reactions. *Am. J. M. Sc.*, 201: 847, 1941.
- HECK, F. J. and HALL, B. E. Leukemoid reactions of the myeloid type. *J. A. M. A.*, 112: 95, 1949.
- KRUMBHAAR, E. B. Leukemoid blood picture in various clinical conditions. *Am. J. M. Sc.*, 172: 519, 1926.
- MEYER, L. M. and ROTTER, S. D. Leukemoid reaction (hyperleukocytosis) in malignancy. *Am. J. Clin. Path.*, 12: 218, 1942.
- JACKSON, H., JR. The protean character of the leukemias and the leukemoid states. *New England J. Med.*, 220: 175, 1939.
- MORRISON, M. An analysis of the blood picture in 100 cases of malignancy. *J. Lab. & Clin. Med.*, 17: 1071, 1932.
- LISA, J. R., SOLOMON, C. and GORDON, E. J. Leukemoid reaction in carcinomatous skeletal and splenic metastases. *Am. J. Cancer*, 40: 227, 1940.
- REICH, C. A case of adenocarcinoma of the sigmoid with lymphatic leukemia blood pictures. *Am. J. Cancer*, 26: 781, 1936.
- SALA, A. M. and STEIN, R. J. Carcinoma of the breast with a condition of the blood simulating chronic lymphatic leukemia. *Arch. Path.*, 23: 531, 1937.
- WINANS, H. M. Leukemoid blood picture in pseudomucinous cyst and papillary adenoma of the ovary. *Am. J. M. Sc.*, 181: 251, 1931.
- KUGELMEIER, L. M. Leukamoide Reaktionen bei Carcinom. *Folia haem.*, 53: 370, 1935.
- WARD, R. G. Secondary or symptomatic leukemia. *Proc. Roy. Soc. Med.*, 7: 126, 1913, 14.
- WINTROBE, M. M. *Clinical Hematology*. 2nd ed. Philadelphia, 1947. Lea & Febiger.
- WHITBY, L. E. H. and BRITTON, C. J. *Disorders of the Blood*. 4th ed. Philadelphia, 1942. Blakiston Co.
- MULLER, A. and WERTHEMANN, A. Unter dem Bilde der sogenannten Leukanämie verlaufende Karzinose des Knochenmarkes bei kleinem verstecktem Mammakarzinom. *Folia haem.*, 46: 429, 1932.
- BICHEL, J. Lymphatic leukemia and lymphatic leukemoid states in cancer of the stomach. *Blood*, 4: 759, 1949.

Sickle Cell Anemia Simulating Poliomyelitis in a White Adult*

ROBERT S. GORDON, M.D. and HORACE T. GARDNER, M.D.

New Haven, Connecticut

Upton, New York

SINCE Cooley and Lee¹ reported the first authentic case of sickle cell anemia in the white race in 1929, some sixteen additional cases have been reported in which no evidence of Negro ancestry could be found.²⁻¹⁷ The great majority of these patients were of Mediterranean extraction, ten being of Italian and four of Greek origin; the others included one of Scotch-Irish and one of German extraction, and one of "midwestern American" origin who had not been further traced. Case reports of Mexican, Puerto Rican and Arabian subjects are excluded because of the frequent admixture with Negroes. The incidence of the sickling trait was found to be 7.3 per cent in a survey of 8,453 Negroes by Diggs et al.¹⁸ Similar studies on over 1,500 white subjects have in no instance uncovered the trait.¹⁸⁻²²

The following case in a young American male of Greek extraction is reported as an additional instance chiefly because of the simulation of acute poliomyelitis by the clinical picture:

CASE REPORT

J. S., a twenty-six year old single engineer of Greek extraction, was admitted to the isolation service of the Grace-New Haven Community Hospital in August, 1949. He had been referred from a local hospital with the tentative diagnosis of poliomyelitis.

Five days prior to the patient's admission a mild upper respiratory infection developed manifested by coryza and dry cough. Two days before admission he was awakened from sleep

by a severe pain in his low back radiating to the flanks. Shortly thereafter he noted severe pain in both knees and aching of the muscles of the thighs and legs. At no time did he have headache or any gastrointestinal disturbance. He was admitted to a local hospital the following morning where he was found to have a temperature of 101°F. and a distended, rigid abdomen without tenderness or abdominal pain. His white blood cell count was 20,000 with 89 per cent neutrophils. A lumbar puncture revealed clear fluid under pressure (360 mm.). The fluid was normal microscopically and chemically. The patient was unable to void and was catheterized. The urine showed albumin 4+ and many granular casts. He was referred to the Grace-New Haven Community Hospital with a tentative diagnosis of transverse myelitis or poliomyelitis.

The patient was considered a normal healthy child until the age of nine when he had a bout of abdominal pain followed with weakness and fatigue. His physician found him to be anemic and he was admitted to a hospital where a diagnosis of Cooley's anemia was made. No sickling preparation was made. He received several transfusions and after discharge was placed on liver and iron which he had taken throughout the subsequent years. In the interim he had gone to school and college and had engaged in vigorous competitive sports without restriction. In 1943 he was told by the Army that he had splenomegaly but was inducted and served for one year in the United States. He had had pneumonia the year before admission, characterized by pleuritic pain. He was hospitalized and treated with penicillin for one week, recovering without sequelae. There were no known anemias or unexplained illnesses in his family.

* From the Department of Internal Medicine and the Section of Preventive Medicine, Yale University School of Medicine, New Haven, Conn.

Physical examination revealed the following: The patient was a normally developed and proportioned, sallow-appearing, young male who was acutely ill. He was apprehensive, breathing rapidly and in obvious pain. The rectal temperature was 102°F., the pulse rate 110 per minute and respirations 36. The blood pressure was 140/80. The skin, lips and nailbeds were pale. There was a slight icterus of the sclerae. The lung fields were clear; the heart was not remarkable. The abdomen was distended and tympanitic but there was no localized tenderness or diminished peristalsis. The liver and spleen could not be palpated. The bladder was distended. The most striking findings were the marked tenderness about the knees and the moderate tenderness and spasm of the paraspinal, thigh and calf musculature. There was no evident weakness or paralysis although motion was limited because of the pain. Sensation was intact; the superficial reflexes and the deep tendon reflexes in the lower extremities were not obtainable. There was no stiffness or rigidity of the neck muscles. Rectal sphincter tone was good.

The laboratory findings were as follows: The admission red blood cell count was 3,720,000, with 9 gm. of hemoglobin. The blood indices were normal. The white blood cell count was 34,000, with 82 per cent neutrophils. There were 29 normoblasts per 100 white cells in the peripheral smear. The reticulocyte count was 5.3 per cent. The red cell fragility was decreased. A sealed preparation of the peripheral blood revealed 10 per cent sickling in three hours and complete sickling in six hours. Following venous stasis for six minutes the sedimentation rate (Wintrobe) of the non-aerated blood was 9.5 mm. per hour as compared to a rate of 52 mm. per hour on the re-aerated specimen. Sickling preparations were made from the patient's immediate family. The sickling trait was demonstrable in two female siblings but was absent in the mother. The father and one other female sibling were not available for study.

Roentgenograms of the skull and long bones were negative. An electrocardiogram was normal. Serum cold agglutinins were absent. The total serum bilirubin was 2.0 mg. per cent, with a one-minute value of .22 mg. per cent. The cephalin-cholesterol flocculation test was 4+, and the serum alkaline phosphatase was 20.6 Bodansky units. These values reverted toward normal after the first week. The total serum cholesterol was 145 mg. per cent, with 45 per cent free

cholesterol. The serum proteins were normal. The initial urinalysis revealed 2+ albumin and four to five red blood cells and four to five white blood cells per high power field, but no casts. These findings subsequently disappeared. A lumbar tap was done and was completely negative except for an initial pressure of 270 mm. water.

Throughout the first two weeks of hospitalization the patient ran a continuous fever between 101° and 103°F. A transient difficulty in voiding was present on admission but catheterization was not considered necessary. On the second hospital day numerous moist rales developed over the right lower lung field, with diminution of breath sounds. X-ray of the chest revealed an infiltration in the right lower lobe suggestive of pneumonitis. There had been no cough, chest pain or further elevation in temperature. Penicillin was given in a total dosage of 600,000 units daily for four days but was without effect and therefore discontinued. The patient was given two 500-cc. whole blood transfusions after the red blood cell count fell to 2.0 million with sickling becoming evident in the counting chamber. The serum bilirubin, however, did not rise. After the first hospital week the abdominal distention, tachypnea and pain in the extremities progressively diminished, the deep tendon reflexes became elicitable and the physical findings in the chest became normal. The patient's temperature gradually fell to normal within the third week and concomitantly all soreness and pain in the limbs disappeared. The red blood count became stabilized at 3.1 million. The patient was discharged on the twenty-second hospital day.

Two months following discharge the patient had completely regained his usual good health; the red blood cell count was 4.2 million with 10.5 gm. of hemoglobin. No nucleated red cells were present in the peripheral blood. A sickling preparation revealed complete sickling only after eighteen hours.

COMMENTS

Any or all of the symptoms presented by this patient have been known to occur in sickle cell anemia. However, the patient's racial extraction and the findings of fever, muscle pain and spasm, areflexia in the lower extremities and the urinary retention occurring in the "poliomyelitis season" were reasonable evidence to suggest the diag-

nosis of poliomyelitis. In addition the hematologic picture with the patient's Mediterranean background was quite compatible with his previous diagnosis of thalassemia—in the absence of a sickling preparation.

Wintrobe²³ has noted a case in which the initial picture simulated poliomyelitis. Central nervous system involvement in sickle cell anemia has been reviewed by Hughes et al.²⁴ Stiffness and pain in the neck, back and legs were not uncommon presenting symptoms in the cases studied. In the majority of instances the cerebrospinal fluid was normal; the abnormal findings included an increase in pressure, sickled red cells, xanthochromia and increase in protein and white cells. The significant pathologic condition consisted of thrombotic occlusion of the smaller blood vessels and dilatation and congestion of the vessels with sickled red cells. The vessels of the meninges and cortical gray matter were primarily involved. Whether there was actual involvement of the central nervous system in the case reported herein cannot be determined. The cerebrospinal fluid pressure, however, was consistently elevated.

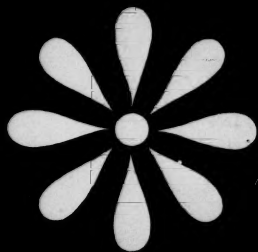
The etiology of the pulmonary infiltration is also obscure. Whether this represented a mild so-called "pneumonic" type of drepanocytic crisis due to intravascular thrombosis which has been described²⁵ or to primary atypical pneumonia is speculative. The patient did not develop cold agglutinins, but even if he had it would have been of doubtful significance in view of the high incidence of cold agglutinins in patients with sickle cell anemia.²⁶

SUMMARY

A case of sickle cell anemia is reported in a white male of Greek extraction during a crisis simulating poliomyelitis, with a brief discussion of the symptomatology.

REFERENCES

- COOLEY, T. B. and LEE, P. Sickle cell anemia in a Greek family. *Am. J. Dis. Child.*, 38: 103, 1929.
- SIGHTS, W. P. and SIMON, S. D. Marked erythrocytic sickling in a white adult, associated with anemia, syphilis, and malaria. *J. Med.*, 12: 177, 1931.
- ROSENFELD, S. and PINGUS, J. B. Occurrence of sickle cell anemia in the white race. *Am. J. M. Sc.*, 184: 674, 1932.
- CLARKE, F. Sickle cell anemia in the white race with report of 2 cases. *Nebraska M. J.*, 17: 376, 1933.
- COOKE, J. V. and MACK, J. K. Sickle cell anemia in a white American family. *J. Pediat.*, 5: 601, 1934.
- HADEN, R. L. and EVANS, F. D. Sickle cell anemia in the white race. *Arch. Int. Med.*, 60: 133, 1937.
- JOHNSON, F. B. and TOWNSEND, E. W. Sickle cell anemia. *South. M. & S. J.*, 99: 377, 1937.
- WEINER, S. B. Sickle cell anemia in an Italian child. *J. Mt. Sinai Hosp.*, 4: 88, 1937.
- PONTONI, L. Sulla eritropatia depaenocitica costituzionale tipo Herrick. *Haematologica*, 20: 657, 1939.
- GREENWALD, L. and BURRETT, J. B. Sickle cell anemia in a white family. *Am. J. M. Sc.*, 199: 768, 1940.
- MALLORY, T. B. Case record of the Massachusetts General Hospital. *New England J. Med.*, 225: 626, 1941.
- WADE, L. J. and STEVENSON, L. D. Necrosis of the bone marrow with fat embolism in sickle cell anemia. *Am. J. Path.*, 17: 47, 1941.
- VANCE, B. M. and FISHER, R. C. Sickle cell disease. *Arch. Path.*, 32: 378, 1941.
- GREENWALD, L., SPIELHOLZ, J. B. and LITWINS, J. Sickling trait in a white adult associated with hemolytic anemia, endocarditis, and malignancy. *Am. J. M. Sc.*, 206: 158, 1943.
- MORRISON, M., SAMWICK, A. A. and LANDSBERG, E. Sickle cell anemia in the white race. *Am. J. Dis. Child.*, 64: 881, 1942.
- OGDEN, M. A. Sickle cell anemia in the white race with report of 2 cases in 2 families. *Arch. Int. Med.*, 71: 164, 1943.
- WOOFER, A. C., DICK, W. S. and BIERRING, W. L. Sickle cell anemia in white patients with ulcers of ankles. *Arch. Int. Med.*, 76: 230, 1945.
- DIGGS, L. W., AHMANN, C. F. and BIBB, J. The incidence and significance of the sickle cell trait. *Ann. Int. Med.*, 7: 769, 1933.
- CARDOZO, W. W. Immunologic studies of sickle cell anemia. *Arch. Int. Med.*, 60: 623, 1937.
- KILLINGSWORTH, W. P. and WALLACE, S. A. Sickle cell anemia in the Southwest. *South. M. J.*, 29: 941, 1936.
- KORB, J. H. and MIYAMOTO, K. Meniscocytosis (latent sickle cell anemia); its incidence in St. Louis. *South. Med. J.*, 20: 912, 1927.
- SYDENSTRICKER, V. P., MULHERIN, W. A. and HOUSEAL, R. W. Sickle cell anemia. *Am. J. Dis. Child.*, 26: 132, 1923.
- WINTROBE, M. M. *Clinical Hematology*. 2nd ed. Philadelphia, 1946. Lea & Febiger.
- HUGHES, J. G., DIGGS, L. W. and GILLESPIE, C. E. Involvement of the nervous system in sickle cell anemia. *J. Pediat.*, 17: 166, 1940.
- YATER, W. M. and HANSMANN, G. H. Sickle cell anemia. *Am. J. M. Sc.*, 191: 474, 1936.
- MCSWEENEY, J. E. J., MERMANN, A. C. and WAGLEY, P. F. Cold hemagglutinins in sickle cell anemia. *Am. J. M. Sc.*, 214: 542, 1947.



**for the pain
that *wasn't* there fol-
lowing Pabalate ther-
apy in arthritis.**

**Para-aminobenzoic
acid 0.3 Gm. (5 gr.),
plus sodium salicy-
late 0.3 Gm. (5 gr.)
provide *higher* sali-
cylate blood levels
on *lower* salicylate
dosage — with *more*
prolonged clinical
relief, and *reduced*
side-effects.**

P

*"...the only drug we have seen
that allays anxiety without
clouding consciousness"*

J.A.M.A. 140:872 (June 25) 1949



Tolserol (Squibb Mephenesin)

- to alleviate pronounced anxiety and tension
- as an adjunct in the treatment of chronic alcoholics

DOSAGE

In anxiety tension states:

As little as 0.5 Gm., given orally every few hours, has produced a good response. However, for optimum effect, 0.75 Gm. or more is given several times a day.

As an adjunct in the treatment of chronic alcoholics:

As much as 3 Gm. orally every four hours has been found useful in the acute stage. This dosage is reduced when the patient becomes more manageable. (If Tolserol is given too soon after the patient drank alcohol, the toxic effect of the alcohol may be potentiated. For this reason, Tolserol should not be administered until six hours have elapsed since the patient drank alcohol.)

Tablets, 0.5 Gm., 0.25 Gm.; Capsules, 0.25 Gm.;
Elixir, 0.1 Gm. per cc.; Solution, 2% (intravenous).

Tolserol (Squibb Mephenesin)

SQUIBB 146 FIFTH AVENUE, NEW YORK 22, NEW YORK
MANUFACTURING CHEMISTS TO THE MEDICAL PROFESSION SINCE 1899

"TOLSEROL" IS A REGISTERED TRADEMARK OF E. R. SQUIBB & SONS

RUTAMINAL*



¹In keeping with newer clinical findings, the rutin content of RUTAMINAL has been increased to 60 mg. per tablet (three times the former rutin content) at no increase in cost to the patient.

*RUTAMINAL is the trademark of Schenley Laboratories, Inc. and designates exclusively its brand of tablets containing rutin, aminophylline, and phenobarbital.

the
protection
of
rutin¹
the
action
of
aminophylline
the
sedation
of
phenobarbital
—for
use
in
selected
cardiovascular
and
diabetic
conditions
in
which
excessive
capillary
fragility
presents
a
complicating
hazard
—bottles
of
100
tablets

schenley laboratories, inc., 350 fifth ave., new york 1, n. y.

© Schenley Laboratories, Inc.

***antibacterial
effects
potentiated***

Biosulfa

A single tablet of this potent new antibacterial agent contains 100,000 units of crystalline penicillin G potassium with 0.25 Gm. each of sulfamerazine and sulfadiazine for additive or synergistic effects. Increased antibacterial activity with low toxicity and ease of administration recommend the use of Biosulfa* tablets for control of numerous human infections caused by penicillin or sulfonamide susceptible organisms.

Supplied in bottles of 50 tablets

**Trademark*

Upjohn

THE UPJOHN COMPANY, KALAMAZOO 99, MICHIGAN

Medicine . . . Produced with care . . . Designed for health

they
deserve
the
best..

Implicit in a happy healthy childhood is maximal nutrition—and one of the essential dietetic guideposts to vigorous adulthood is adequate vitamin C^{1,2,3} (1/4-4 oz. for infants up to 1 year;^{10,11} 4-8 oz. for older children).⁴ Fortunately, most every youngster likes the taste of Florida orange juice and the "lift" its easily assimilable fruit sugars* provide.⁶ It is well-tolerated and virtually non-allergenic.³ And, under modern techniques of processing and storage—it is possible for citrus fruits and juices (whether fresh, canned or frozen) to retain their ascorbic acid content,^{5,8} and their pleasing flavor,⁷ in very high degree and over long periods.

FLORIDA CITRUS COMMISSION • LAKELAND, FLORIDA

Citrus fruits—among the richest known sources of Vitamin C—also contain vitamins A and B, readily assimilable natural fruit sugars, and other factors, such as iron, calcium, citrates and citric acid.

... plenty of citrus fruit

References

1. Clinical Nutrition: ed. by N. Jolliffe et al., Hoeber, 1950.
2. Hanks, M. T.: Diet and Dental Health, Chicago Univ. Press, 1933.
3. Jeans, P. C.: J.A.M.A., 143:908, 1950.
4. Joslin, C. L. and Bradley, J. E.: Personal communication.
5. Krehl, W. A. and Cowgill, G. R.: Food Research, 15:179, 1950.
6. Mc Lester, J. S.: Nutrition and Diet in Health and Disease, Saunders, Phila., 4th ed., 1944.
7. Moore, E. L. et al.: J. Home Econ., 37:290, 1948.
8. Roy, W. R. and Russell, H. E.: Food Industries, 20:1764, 1948.
9. Sherman, H. C.: Chemistry of Food and Nutrition, Macmillan, 7th ed., 1948.
10. Silverman, A. C.: New York J. Med., 47:1867, 1947.
11. Stevenson, S. S.: J. Pediat., 31:616, 1947.



FLORIDA
Oranges • Grapefruit
Tangerines





In Acute Exanthems —

The fever of measles, the pruritus of chickenpox or the sore throat of scarlet fever will find pleasant relief in Aspergum.

For childhood's pains and fevers, Aspergum is ideal—it is willingly accepted by the patient and it presents acetylsalicylic acid in a rapidly effective form.

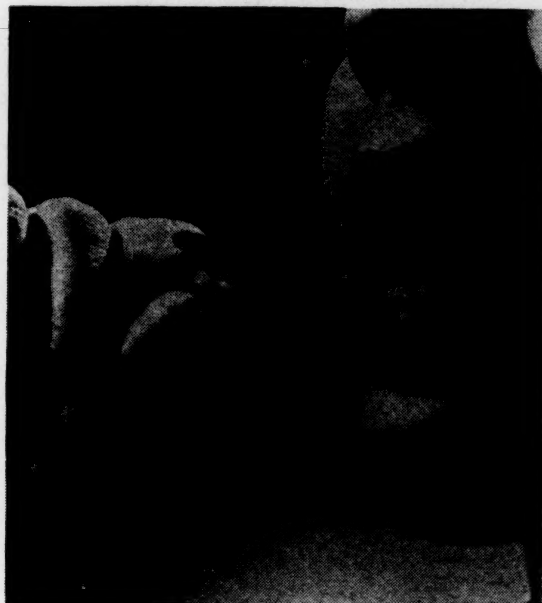
Aspergum is promoted ethically; is not advertised to the public.

Each pleasantly flavored tablet of Aspergum contains $3\frac{1}{2}$ grains of acetylsalicylic acid—a dosage form uniquely fitted to childhood requirements.

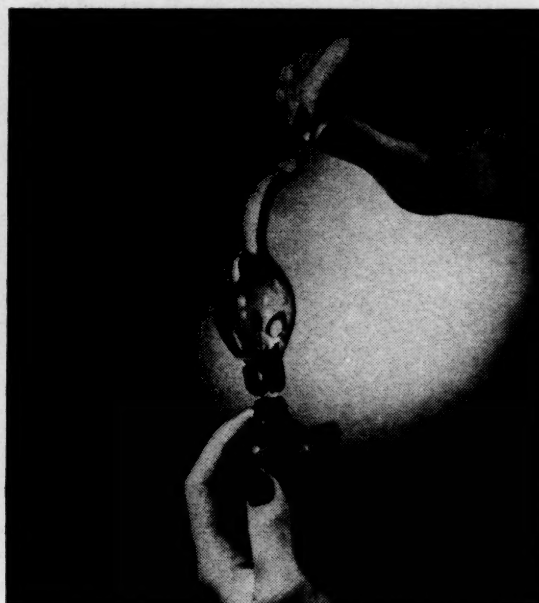
aspergum

Versatile Penicillin

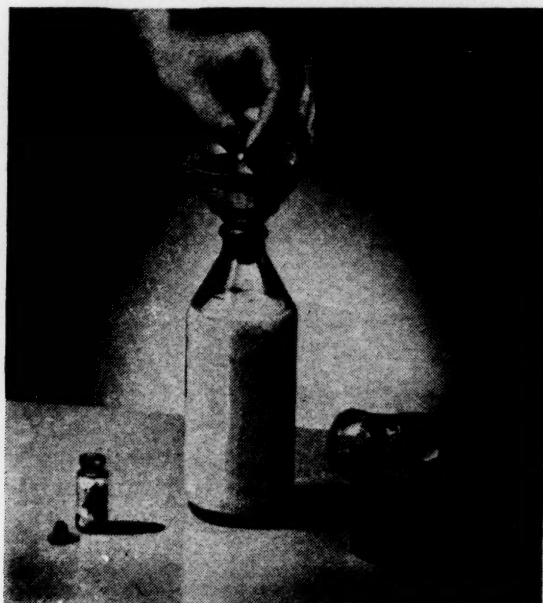
STABLE, CRYSTALLINE POTASSIUM PENICILLIN G by Mouth, by Lung, by G. I. Tract



by mouth: Oral **PENALEV**® tablets (50,000 or 100,000 units) are rapidly absorbed, quickly create effective penicillin blood levels.



by lung: Potent penicillin G aerosol solutions can readily be prepared by dissolving **PENALEV** tablets in water or normal saline.



PENALEV®

soluble tablets crystalline

Potassium Penicillin G

by G. I. tract: **PENALEV** tablets dissolve promptly in milk, fruit juices, or infant formulas, without appreciably changing their taste • **PENALEV** soluble tablets crystalline potassium penicillin G: 50,000 units in vials of 12, boxes of 24 and bottles of 100 • 100,000 units in vials of 12 and bottles of 100.

Sharp & Dohme, Philadelphia 1, Pa.



For the many patients who require more than iron alone to show satisfactory progress in secondary anemia, Livitamin Capsules offer sound therapy.

By correcting anorexia and faulty intestinal absorption, the vicious spiral so frequently responsible for anemia is broken.

Supplying generous amounts of vitamin B₁₂ together with iron and other factors of the B complex, Livitamin Capsules aid in maintaining the appetite and normal gastrointestinal function.

Livitamin is well tolerated and may be given to children as well as to adults. This complete approach to hypochromic anemia produces gratifying and prompt improvement in both the blood picture and clinical manifestations. Available also as Livitamin with Iron (in liquid form).

THE S. E. MASSENGILL COMPANY
Bristol, Tenn.-Va.
NEW YORK • SAN FRANCISCO • KANSAS CITY



Each capsule contains:

Desiccated Liver.....	0.5 Gm.
Ferrous Sulfate.....	.125 Gm.
(equivalent to 25 mg. elemental iron)	
Thiamine Hydrochloride.....	3 mg.
Riboflavin.....	3 mg.
Nicotinamide.....	10 mg.
Pyridoxine.....	0.5 mg.
Calcium Pantothenate.....	2 mg.
B ₁₂	2 micrograms

Available on prescription
in all pharmacies.
Write for sample and literature.



WYDASE IN RECENT CLINICAL APPLICATIONS
Part of a series on its expanding uses.

Wyeth
 ®

**LOCAL ANESTHESIA
 IN TONSILLECTOMY**

FROM A RECENT REPORT:¹

- Wydase is a safe adjunct to solutions used for local anesthesia in tonsillectomy and in other surgical procedures.
- Rapid diffusion enables the surgeon to begin the operation immediately after injection and to use less material.
- Healing is hastened because there is less tissue reaction.
- There were no untoward reactions, local or general.

1. Heinberg, C.J.: Eye, Ear, Nose & Throat Monthly 30:31 (Jan.) 1951.

In Hypodermoclysis—WYDASE prevents pain from stretching of tissues, facilitates introduction of fluids when intravenous administration is impractical.

In Local Anesthesia—WYDASE, added to the local anesthetic, contributes depth and facility to anesthesia, minimizes tissue distortion.

Highly purified WYDASE in dry form is stable indefinitely; keeps in sterile solution in a cool place for 2 weeks—refrigeration unnecessary.

LYOPHILIZED

WYDASE*

HYALURONIDASE, WYETH

*Trade-mark

WYETH INCORPORATED, PHILADELPHIA 2, PA.

IN
THE
AIM
TOWARD



Lessening Illness in the Aged

By maintaining complete adequacy of the diet during advancing years, considerable can be accomplished in reducing the frequency of illness in the aged population and in favorably influencing the mental state of the geriatric patient. In particular, ample intake of protein, vitamins, and minerals is needed for preventing many somatic and psychic symptoms of malnutrition often observed in the aged.¹

The dietary supplement, Ovaltine in milk, is a reliable aid for supporting the nutritional state of the elderly patient.

This nutritious beverage richly provides biologically complete protein, minerals—especially calcium and iron—and all the vitamins considered essential. Used in the recommended amount, it can readily supplement even poor diets to full nutrient adequacy. It is easily digestible, invigorating, and pleasingly palatable.

Note the wealth of nutrients furnished by Ovaltine in milk, as shown by the table given below.

1. Thewlis, M., and Gale, E. T.: Ambulatory Care of the Aged, *Geriatrics*, 5:331 (Nov.-Dec.) 1950.

THE WANDER COMPANY, 360 N. MICHIGAN AVE., CHICAGO 1, ILL.

Ovaltine

Three servings daily of Ovaltine, each made of ½ oz. of Ovaltine and 8 oz. of whole milk,* provide:

PROTEIN	32 Gm.	VITAMIN A	3000 I.U.
FAT	32 Gm.	VITAMIN B ₁	1.16 mg
CARBOHYDRATE	65 Gm.	RIBOFLAVIN	2.0 mg
CALCIUM	1.12 Gm.	NIACIN	6.8 mg
PHOSPHORUS	0.94 Gm.	VITAMIN C	30.0 mg.
IRON	12 mg.	VITAMIN D	417 I.U.
COPPER	0.5 mg.	CALORIES	676

*Based on average reported values for milk.

Two kinds, Plain and Chocolate Flavored. Serving for serving, they are virtually identical in nutritional content.



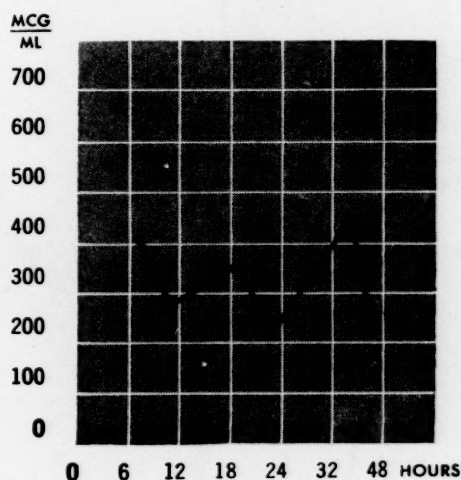
*In the selection of an antibiotic
for URINARY ANTISEPSIS*

high urinary levels
rapidly achieved
and easily maintained } *are a critical requirement*

CRYSTALLINE Terramycin

HYDROCHLORIDE

concentration of Terramycin in the urine following divided oral doses: 0.5 Gm. q 6 h.³



1. Schoenbach, E. B., Bryer, M. S., and Long, P. H.: Ann. New York Acad. Sc. 53:245 (Sept. 15) 1950.

2. Welch, H.; Hendricks, F. D.; Price, C. W., and Randall, W. A.: J. A. Ph. A. (Sc. Ed.) 39:185 (Apr.) 1950.

3. Welch, H.: Ann. New York Acad. Sc. 53:253 (Sept. 15) 1950.

This newest of the broad-spectrum antibiotics is stable and active in the urine. High levels are rapidly achieved and easily maintained by oral administration. Within one-half hour after a single 2 Gm. dose, detectable amounts have appeared in the urine,¹ and a single 0.5 Gm. dose has been shown to produce high concentrations lasting twenty-four hours.² When multiple doses are given, continuous urinary concentrations of Terramycin in the range of 300-400 mcg./ml. are obtained, as shown in the accompanying chart.³

These observations are given added significance by the highly satisfactory clinical experience and the prompt response obtained with Terramycin in a wide range of infections of the urinary tract.

Supplied: 250 mg. capsules, bottles of 16 and 100;
100 mg. capsules, bottles of 25 and 100;
50 mg. capsules, bottles of 25 and 100.

Antibiotic Division

Pfizer

CHAS. PFIZER & CO., INC., Brooklyn 6, N. Y.

appetite
must be controlled



"The greatest problem in preventive medicine in the United States today is obesity."¹ And today it is well-known that

*"The only way to counteract obesity . . . is by a restriction of food intake."*²

'Dexedrine' Sulfate controls appetite, making it easy for the patient to avoid overeating and thus to lose weight safely without the use (and risk) of such potentially dangerous drugs as thyroid.

In weight reduction 'Dexedrine' *"is the drug of choice because of its effectiveness and the low incidence of undesirable side effects."*¹

Smith, Kline & French Laboratories • Philadelphia

Dexedrine* Sulfate tablets • elixir

The most effective drug for control of appetite in weight reduction

*T.M. Reg. U.S. Pat. Off.

1. Walker, W.J.: Obesity as a Problem in Preventive Medicine, U.S. Armed Forces M.J. 1:393, 1950.

2. John, H.J.: Dietary Invalidism, Ann. Int. Med. 32:595, 1950.

SIXTIETH

The American Journal of Surgery

ANNIVERSARY

SPEAKS



with the authority of 60 years'
SERVICE TO SURGERY

IT is more significant to be distinguished by achievement than by age. We have endeavored to use our years well in the interests of surgery. Indicative of our continuing efforts is the announcement, in this our 60th year, of such new departments as Modern Operative Technics, Practical Surgical Suggestions, Streamlined Articles and Obstetric Clinic. Since 1891, leading surgeons have respected the scope of editorial content and authority of our many leading contributors on pertinent subjects in surgery.



We invite you to join our more than 30,000 surgeon-readers who recognize in THE AMERICAN JOURNAL OF SURGERY an authoritative voice in the art and practice of surgery.

THE AMERICAN JOURNAL OF SURGERY publishes regularly the proceedings of the American Association for the Surgery of Trauma and of The American Proctologic Society.

THE AMERICAN JOURNAL OF SURGERY, INC.
49 West 43rd Street, New York 19, N. Y.

Gentlemen:

I am enclosing my payment of \$12.00 for one year's subscription to THE AMERICAN JOURNAL OF SURGERY. Please send to:
(add \$3.00 for foreign postage)

NAME _____

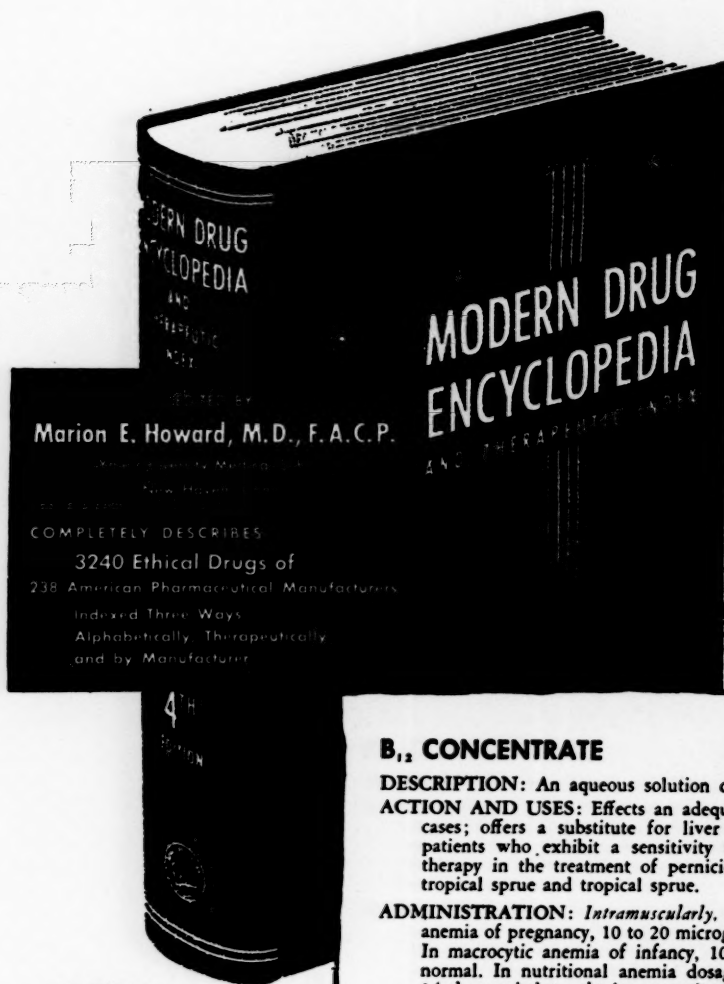
STREET _____

CITY _____ ZONE _____ STATE _____

■ EIGHTEEN NINETY ONE TO NINETEEN FIFTY ONE ■

A MEDICAL BEST SELLER!

SECOND PRINTING



Marion E. Howard, M.D., F.A.C.P.

COMPLETELY DESCRIBES

3240 Ethical Drugs of
238 American Pharmaceutical Manufacturers
Indexed Three Ways
Alphabetically, Therapeutically
and by Manufacturer

1949 Edition
Bound in Red Fabricoid
1,200 pages, Size 2" x 6" x 9"
Price Postpaid \$12 U.S.A. —
\$14 Foreign

Doctors' Comments

"Please accept my congratulations on your excellent publication on Modern Drugs." K.S.G., M.D., Durham, N. C.

"I am finding it very useful." L.I.Y., M.D., Winona, Minn.

"Put my name down to send me a new one every time it comes off the press." D.H.A., M.D., Memphis, Tenn.

"I think this is one of the best publications in print." W.S., M.D., Augusta, Ga.

Typical Description

B₁₂ CONCENTRATE

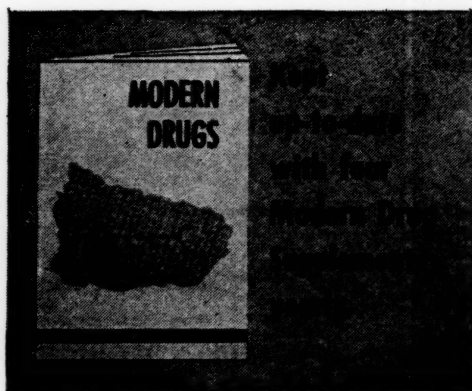
Hematopoietic

(Armour)

DESCRIPTION: An aqueous solution containing 10 micrograms of vitamin B₁₂ per cc
ACTION AND USES: Effects an adequate hematopoietic response in pernicious anemia cases; offers a substitute for liver therapy in the treatment of pernicious anemia patients who exhibit a sensitivity to liver extract. An important adjunct to liver therapy in the treatment of pernicious anemia, nutritional macrocytic anemia, non-tropical sprue and tropical sprue.

ADMINISTRATION: *Intramuscularly*, preferably in the gluteal muscle. In macrocytic anemia of pregnancy, 10 to 20 micrograms once a week until termination of pregnancy. In macrocytic anemia of infancy, 10 to 20 micrograms until blood count returns to normal. In nutritional anemia dosage may vary from 6 to 100 micrograms over a 14 day period to obtain an optimal response. In most pernicious anemia cases 25 micrograms per week results in an optimal response.

SUPPLY: B₁₂ CONCENTRATE—Vials, rubber-capped, 10 cc.



Drug Publications, Inc.
49 West 45th St., New York 19, N. Y.

Enclosed is the sum of twelve dollars (\$12 U.S.A.) for which please send me postpaid the new Fourth Edition of the MODERN DRUG ENCYCLOPEDIA AND THERAPEUTIC INDEX AND MODERN DRUGS.

Name.....

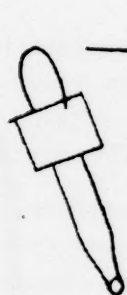
Address.....

City..... Zone..... State.....

U.S.A. \$12

Foreign \$14

Therapeutic penicillin dosage
is EASY, PLEASANT with



→ DROP-CILLIN

50,000 UNITS* IN A DROPPERFUL

Available in 9cc. bottle
containing 600,000 units.



→ DRAM-CILLIN

100,000 UNITS* IN A TEASPOONFUL

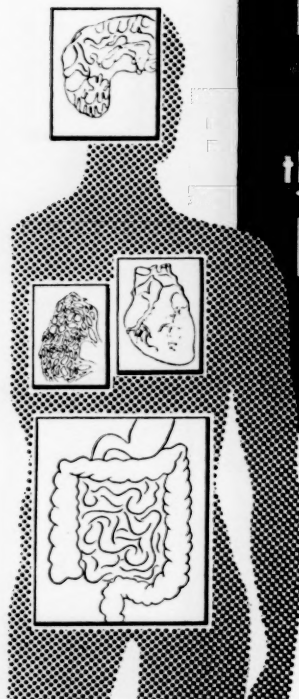
Available in 60cc. bottle
containing 1,200,000 units.

Both with a palatable
vanilla flavor.

* BUFFERED PENICILLIN
& POTASSIUM

WHITE LABORATORIES, INC.

Pharmaceutical Manufacturers, Newark 7, N.J.



PERTENAL

treats more
than the pressure in
hypertension
...also controls
harassing symptoms

Each PERTENAL tablet contains:
 VERATRUM VIRIDE 100 mg.
 HOMATROPINE METHYL BROMIDE . 2.5 mg.
 MANNITOL HEXANITRATE 30 mg.
 PHENOBARBITAL 15 mg.

so that the *whole patient* feels better, more normal, more comfortable.

PERTENAL produces a... **substantial, sustained, safe descent in pressure** via dual hypotensive action... Heart load is eased.

relaxes gastro-intestinal tension — relieving pain, spasm and other g.i. disturbances which may tend to aggravate hypertension.

controls other symptoms that plague the hypertensive and send the pressure soaring — headache, nervousness, fear, insomnia, vertigo. Patients feel better as soon as PERTENAL therapy is started.

write for PERTENAL SAMPLES and literature.



CROOKES LABORATORIES, INC.
305 EAST 45 ST., NEW YORK, N. Y.

Back Issues Wanted

(MUST BE IN PERFECT CONDITION)

THE AMERICAN JOURNAL OF MEDICINE

will pay

\$1.00 per copy for the following issues:

July 1946	August 1947
August 1946	October 1947
September 1946	November 1947
October 1946	January 1948
November 1946	February 1948
January 1947	March 1948
February 1947	July 1948
March 1947	June 1949
April 1947	August 1949
May 1947	September 1949
June 1947	November 1949

February 1950

Send to

THE YORKE PUBLISHING COMPANY, Inc.
49 West 45th Street
New York 19, N. Y.

a new therapy for tetanus...

Descriptive literature
and complimentary
supply of

Dioloxol

Brand of mephenesin
TABLETS, CAPSULES, ELIXIR
available from

G. W. Carnrick Co.
NEWARK 1, NEW JERSEY

Recent clinical reports^{1,2,3}
have furnished initial
evidence that mephenesin
affords positive and
prompt relief of spasms
of tetanus in moderate
cases when given orally
or per rectum.

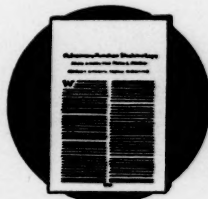


1. Godman, H. E., and Adriani, J.:
J.A.M.A. 141:754, 1949.
2. Fox, P. P., and Banton, A. H.:
Brit. M. J.: 4653:607, 1950.
3. Moseley, V., Coleman, R. R., and
Ellison, H. J.: J. South Carolina
Med. Assn. 46:311, 1950.

DNJ 11

CAN YOU ANSWER THESE VITAL PULMONARY FUNCTION QUESTIONS?

- Is there a consistent relationship between vital capacity and dyspnea?
- In emphysema, what is the correlation between expiration time, shortness of breath and maximum breathing capacity?
- What is the best method of measuring alveolar air?
- What is the minimum maximum breathing capacity necessary, following operation to assure freedom from dyspnea?
- Does thoracoplasty really reduce ventilation function?
- Are pulmonary function tests valuable in pneumothorax?
- How much does phrenic nerve interruption lower the MBC?
- Does pneumoperitoneum reduce MBC sufficiently to be contraindicated?
- Why are repeated pulmonary function tests a must in the post-operative follow-up of pulmonary resection?
- Why is separate reserve air determination so important?



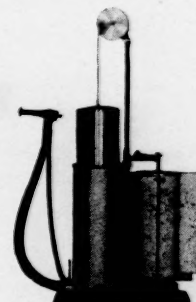
THIS NEW REPRINT HAS THE ANSWERS
BY JOHN J. CURRY AND FRANK S. ASHBURN
of Georgetown Univ. Medical Center entitled PULMONARY FUNCTION STUDIES IN SURGERY. The above questions and many more are given in this latest reprint. Collins equipment pictured here have contributed greatly to the simplicity of pulmonary function studies. Ask for present prices and descriptive literature.

WRITE FOR YOUR FREE COPY TODAY

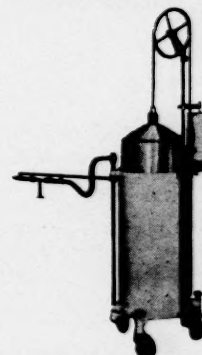
WARREN E. COLLINS, INC.

Specialists in Respiration Apparatus

555 Huntington Ave., Boston 15, Mass.



Collins Respirometer



Collins Chain Compensated Gasometer

No activity
pause
at her
menopause



Your patient may continue her normal activities even to the extent of keeping pace with her daughter. She will be greatly encouraged, especially when the effectiveness of therapy measures up to expectations. In estrogen therapy an especially useful product is:

BENZESTROL

2,4 (p-hydroxyphenyl) -3-ethyl hexane

"Liver function tests, blood studies and urine examinations showed no toxic effects of the synthetic substance BENZESTROL"

Supplied:

Oral: *Benzestrol* Tablets
0.5 Mg., 1.0 Mg., 100's & 1000's, 2 Mg.,
5 Mg. — 50's — 100's — 1000's.

Benzestrol Elixir:
15 Mg. per fluid ounce, Pint Bottles.

Intramuscular: *Benzestrol* Solution in Oil;
Aqueous Suspension with 5% Benzyl Alcohol
5.0 Mg. per cc. 10cc Vials.

Local: *Benzestrol* Vaginal Tablets
0.5 Mg. 100's.

AVERAGE DOSE: Menopause — 2 to 3 Mg. daily
orally or $\frac{1}{2}$ to 1cc parenterally every 5 days.

Professional Samples and Literature upon Request



NOTE:

Frequently, medication other than estrogens may be required during the menopause. Pleasant tasting Elixir Benzestrol is compatible with many substances.

*Reference: MacBryde, C. M., et al., *A New Synthetic Estrogen*, J.A.M.A., 123: 261; 264 (1937) 63.

Schieffelin & Co. 20 Cooper Square, New York 3, N. Y.

